

Description

BIOINFORMATICALLY DETECTABLE GROUP OF NOVEL HIV REGULATORY GENES AND USES THEREOF

BACKGROUND OF INVENTION

CONTINUATION STATEMENT

[0001] This application is a continuation of U.S. Provisional Patent Application Serial No 60411230, filed 17-Jan-03, entitled "Bioinformatically Detectable Group of Novel HIV Regulatory Genes and Uses of Thereof ", and is a continuation of U.S. Patent Application Serial No. 10604944, filed 28-Aug-03, entitled "Bioinformatically Detectable Group of Novel HIV Regulatory Genes and Uses of Thereof ", and is a continuation in part of U.S. Provisional Patent Application Serial No. 60441241, filed 17-Jan-03, entitled "Bioinformatically Detectable Group of Novel Vaccinia Regulatory Genes and Uses of Thereof ", and is a continuation in part of U.S. Patent Application Serial No. 10604943,

filed 28-Aug-03, entitled "Bioinformatically Detectable Group of Novel Vaccinia Regulatory Genes and Uses of Thereof", and is a continuation in part of U.S Patent Application Serial No. 10604942, filed 27-Aug-03, entitled "Bioinformatically Detectable Group of Novel Viral Regulatory Genes and Uses of Thereof", and is a continuation in part of U.S Patent Application Serial No. 10604945, filed 27-Aug-03, entitled "Bioinformatically Detectable Group of Novel Viral Regulatory Genes and Uses of Thereof ", and is a continuation in part of U.S Provisional Patent Application Serial No 60457788, filed 27-Mar-03, entitled " Bioinformatically Detectable Group of Novel Viral Regulatory Genes and Uses of Thereof ", and is a continuation in part of U.S Patent Application Serial No. 10310188, filed 5-Dec-02, entitled "Bioinformatically Detectable Group of Novel Viral Regulatory Genes and Uses of Thereof ", and is a continuation in part of U.S Patent Application Serial No. 10303778, filed 26-Nov-02, entitled "Bioinformatically Detectable Group of Novel Viral Regulatory Genes and Uses of Thereof", and is a continuation in part of U.S Patent Application Serial No. 10604984, filed 29-Aug-03, entitled "Bioinformatically Detectable Group of Novel Viral Regulatory Genes and Uses of Thereof", the disclosures of

which applications are all hereby incorporated by reference and claims priority therefrom.

FIELD OF THE INVENTION

[0002] The present invention relates to a group of bioinformatically detectable novel viral RNA regulatory genes, here identified as "viral genomic address messenger" or "VGAM" genes.

DESCRIPTION OF PRIOR ART

[0003] Small RNAs are known to perform diverse cellular functions, including post-transcriptional gene expression regulation. The first two such RNA genes, Lin-4 and Let-7, were identified by genetic analysis of *Caenorhabditis Elegans* (*Elegans*) developmental timing, and were termed short temporal RNA (stRNA) (Wightman, B., Ha, I., Ruvkun, G., *Cell* 75, 855 (1993); Erdmann, V.A. et al., *Nucleic Acids Res.* 29, 189 (2001); Lee, R. C., Feinbaum, R. L., Ambros, V., *Cell* 75, 843 (1993); Reinhart, B. et al., *Nature* 403, 901 (2000)).

[0004] Lin-4 and Let-7 each transcribe a ~22 nucleotide (nt) RNA, which acts as a post transcriptional repressor of target mRNAs, by binding to elements in the 3'-untranslated region (UTR) of these target mRNAs, which are complimen-

tary to the 22 nt sequence of Lin-4 and Let-7 respectively. While Lin-4 and Let-7 are expressed at different developmental stage, first larval stage and fourth larval stage respectively, both specify the temporal progression of cell fates, by triggering post-transcriptional control over other genes (Wightman, B., Ha, I., Ruvkun, G., Cell 75, 855 (1993); Slack et al., Mol.Cell 5 ,659 (2000)). Let-7 as well as its temporal regulation have been demonstrated to be conserved in all major groups of bilaterally symmetrical animals, from nematodes, through flies to humans (Pasquinelli, A., et al. Nature 408 ,86 (2000)).

[0005] The initial transcription product of Lin-4 and Let-7 is a ~60–80nt RNA, the nucleotide sequence of the first half of which is partially complimentary to that of its second half, therefore allowing this RNA to fold onto itself, forming a "hairpin structure". The final gene product is a ~22nt RNA, which is "diced" from the above mentioned "hairpin structure", by an enzyme called Dicer, which also apparently also mediates the complimentary binding of this ~22nt segment to a binding site in the 3' UTR of its target gene.

[0006] Recent studies have uncovered 93 new genes in this class, now referred to as micro RNA or miRNA genes, in genomes of Elegans, Drosophileia, and Human

(Lagos-Quintana, M., Rauhut, R., Lendeckel, W., Tuschl, T., Science 294 ,853 (2001); Lau, N.C., Lim, L.P., Weinstein, E.G., Bartel, D.P., Science 294 ,858 (2001); Lee, R.C., Ambros, V., Science 294 ,862 (2001). Like the well studied Lin-4 and Let-7, all newly found MIR genes produce a ~60-80nt RNA having a nucleotide sequence capable of forming a "hairpin structure". Expressions of the precursor ~60-80nt RNA and of the resulting diced ~22nt RNA of most of these newly discovered MIR genes have been detected.

[0007] Based on the striking homology of the newly discovered MIR genes to their well-studied predecessors Lin-4 and Let-7, the new MIR genes are believed to have a similar basic function as that of Lin-4 and Let-7: modulation of target genes by complimentary binding to the UTR of these target genes, with special emphasis on modulation of developmental control processes. This is despite the fact that the above mentioned recent studies did not find target genes to which the newly discovered MIR genes complementarily bind. While existing evidence suggests that the number of regulatory RNA genes "may turn out to be very large, numbering in the hundreds or even thousands in each genome", detecting such genes is challeng-

ing (Ruvkun G., "Perspective: Glimpses of a tiny RNA world", Science 294 ,779 (2001)).

[0008] The ability to detect novel RNA genes is limited by the methodologies used to detect such genes. All RNA genes identified so far either present a visibly discernable whole body phenotype, as do Lin-4 and Let-7 (Wightman et. al., Cell 75, 855 (1993); Reinhart et al., Nature 403, 901 (2000)), or produce significant enough quantities of RNA so as to be detected by the standard biochemical genomic techniques, as do the 93 recently detected miRNA genes. Since a limited number clones were sequenced by the researchers discovering these genes, 300 by Bartel and 100 by Tuschl (Bartel et. al., Science 294 ,858 (2001); Tuschl et. al., Science 294 ,853 (2001)), the RNA genes found can not be much rarer than 1% of all RNA genes. The recently detected miRNA genes therefore represent the more prevalent among the miRNA gene family.

[0009] Current methodology has therefore been unable to detect RNA genes which either do not present a visually discernable whole body phenotype, or are rare (e.g. rarer than 0.1% of all RNA genes), and therefore do not produce significant enough quantities of RNA so as to be detected by standard biochemical technique. To date, miRNA have not

been detected in viruses.

SUMMARY OF INVENTION

[0010] The present invention relates to a novel group of bioinformatically detectable, viral regulatory RNA genes, which repress expression of host target host genes, by means of complementary hybridization to binding sites in untranslated regions of these host target host genes. It is believed that this novel group of viral genes represent a pervasive viral mechanism of attacking hosts, and that therefore knowledge of this novel group of viral genes may be useful in preventing and treating viral diseases.

[0011] In various preferred embodiments, the present invention seeks to provide improved method and system for detection and prevention of viral disease, which is mediated by this group of novel viral genes.

[0012] Accordingly, the invention provides several substantially pure nucleic acids (e.g., genomic nucleic acid, cDNA or synthetic nucleic acid) each encoding a novel viral gene of the VGAM group of gene, vectors comprising the nucleic acids, probes comprising the nucleic acids, a method and system for selectively modulating translation of known "target" genes utilizing the vectors, and a method and system for detecting expression of known "target"

genes utilizing the probe.

[0013] By "substantially pure nucleic acid" is meant nucleic acid that is free of the genes which, in the naturally-occurring genome of the organism from which the nucleic acid of the invention is derived, flank the genes discovered and isolated by the present invention. The term therefore includes, for example, a recombinant nucleic acid which is incorporated into a vector, into an autonomously replicating plasmid or virus, or into the genomic nucleic acid of a prokaryote or eukaryote at a site other than its natural site; or which exists as a separate molecule (e.g., a cDNA or a genomic or cDNA fragment produced by PCR or restriction endonuclease digestion) independent of other sequences. It also includes a recombinant nucleic acid which is part of a hybrid gene encoding additional polypeptide sequence.

[0014] "Inhibiting translation" is defined as the ability to prevent synthesis of a specific protein encoded by a respective gene, by means of inhibiting the translation of the mRNA of this gene. "Translation inhibitor site" is defined as the minimal nucleic acid sequence sufficient to inhibit translation.

[0015] There is thus provided in accordance with a preferred em-

embodiment of the present invention a bioinformatically detectable novel viral gene encoding substantially pure nucleic acid wherein: RNA encoded by the bioinformatically detectable novel viral gene is about 18 to about 24 nucleotides in length, and originates from an RNA precursor, which RNA precursor is about 50 to about 120 nucleotides in length, a nucleotide sequence of a first half of the RNA precursor is a partial inversed-reversed sequence of a nucleotide sequence of a second half thereof, a nucleotide sequence of the RNA encoded by the novel viral gene is a partial inversed-reversed sequence of a nucleotide sequence of a binding site associated with at least one host target gene, and a function of the novel viral gene is bioinformatically deducible.

[0016] There is further provided in accordance with another preferred embodiment of the present invention a method for anti-viral treatment comprising neutralizing said RNA.

[0017] Further in accordance with a preferred embodiment of the present invention the neutralizing comprises: synthesizing a complementary nucleic acid molecule, a nucleic sequence of which complementary nucleic acid molecule is a partial inversed-reversed sequence of said RNA, and transfecting host cells with the complementary nucleic

acid molecule, thereby complementarily binding said RNA.

[0018] Further in accordance with a preferred embodiment of the present invention the neutralizing comprises immunologically neutralizing.

[0019] There is still further provided in accordance with another preferred embodiment of the present invention a bioinformatically detectable novel viral gene encoding substantially pure nucleic acid wherein: RNA encoded by the bioinformatically detectable novel viral gene includes a plurality of RNA sections, each of the RNA sections being about 50 to about 120 nucleotides in length, and including an RNA segment, which RNA segment is about 18 to about 24 nucleotides in length, a nucleotide sequence of a first half of each of the RNA sections encoded by the novel viral gene is a partial inversed-reversed sequence of nucleotide sequence of a second half thereof, a nucleotide sequence of each of the RNA segments encoded by the novel viral gene is a partial inversed-reversed sequence of the nucleotide sequence of a binding site associated with at least one target host gene, and a function of the novel viral gene is bioinformatically deducible from the following data elements: the nucleotide sequence of the RNA encoded by the novel viral gene, a nucleotide sequence of

the at least one target host gene, and function of the at least one target host gene.

[0020] Further in accordance with a preferred embodiment of the present invention the function of the novel viral gene is bioinformatically deducible from the following data elements: the nucleotide sequence of the RNA encoded by the bioinformatically detectable novel viral gene, a nucleotide sequence of the at least one target host gene, and a function of the at least one target host gene.

[0021] Still further in accordance with a preferred embodiment of the present invention the RNA encoded by the novel viral gene complementarily binds the binding site associated with the at least one target host gene, thereby modulating expression of the at least one target host gene.

[0022] Additionally in accordance with a preferred embodiment of the present invention the binding site associated with at least one target host gene is located in an untranslated region of RNA encoded by the at least one target host gene.

[0023] Moreover in accordance with a preferred embodiment of the present invention the function of the novel viral gene is selective inhibition of translation of the at least one target host gene, which selective inhibition includes comple-

mentary hybridization of the RNA encoded by the novel viral gene to the binding site.

[0024] Further in accordance with a preferred embodiment of the present invention the invention includes a vector including the DNA.

[0025] Still further in accordance with a preferred embodiment of the present invention the invention includes a method of selectively inhibiting translation of at least one gene, including introducing the vector.

[0026] Moreover in accordance with a preferred embodiment of the present invention the introducing includes utilizing RNAi pathway.

[0027] Additionally in accordance with a preferred embodiment of the present invention the invention includes a gene expression inhibition system including: the vector, and a vector inserter, functional to insert the vector into a cell, thereby selectively inhibiting translation of at least one gene.

[0028] Further in accordance with a preferred embodiment of the present invention the invention includes a probe including the DNA.

[0029] Still further in accordance with a preferred embodiment of the present invention the invention includes a method of

selectively detecting expression of at least one gene, including using the probe.

[0030] Additionally in accordance with a preferred embodiment of the present invention the invention includes a gene expression detection system including: the probe, and a gene expression detector functional to selectively detect expression of at least one gene.

[0031] Further in accordance with a preferred embodiment of the present invention the invention includes an anti-viral substance capable of neutralizing the RNA.

[0032] Still further in accordance with a preferred embodiment of the present invention the neutralizing includes complementarily binding the RNA.

[0033] Additionally in accordance with a preferred embodiment of the present invention the neutralizing includes immunologically neutralizing.

[0034] Moreover in accordance with a preferred embodiment of the present invention the invention includes a method for anti-viral treatment including neutralizing the RNA.

[0035] Further in accordance with a preferred embodiment of the present invention the neutralizing includes: synthesizing a complementary nucleic acid molecule, a nucleic sequence of which complementary nucleic acid molecule is a partial

inversed–reversed sequence of the RNA, and transfecting host cells with the complementary nucleic acid molecule, thereby complementarily binding the RNA.

[0036] Still further in accordance with a preferred embodiment of the present invention the neutralizing includes immuno–logically neutralizing.

BRIEF DESCRIPTION OF DRAWINGS

[0037] Fig. 1 is a simplified diagram illustrating a mode by which viral genes of a novel group of viral genes of the present invention, modulate expression of known host target genes;

[0038] Fig. 2 is a simplified block diagram illustrating a bioinformatic gene detection system capable of detecting genes of the novel group of genes of the present invention, which system is constructed and operative in accordance with a preferred embodiment of the present invention;

[0039] Fig. 3 is a simplified flowchart illustrating operation of a mechanism for training of a computer system to recognize the novel genes of the present invention, which mechanism is constructed and operative in accordance with a preferred embodiment of the present invention;

[0040] Fig. 4A is a simplified block diagram of a non–coding genomic sequence detector constructed and operative in ac–

cordance with a preferred embodiment of the present invention;

[0041] Fig. 4B is a simplified flowchart illustrating operation of a non-coding genomic sequence detector constructed and operative in accordance with a preferred embodiment of the present invention;

[0042] Fig. 5A is a simplified block diagram of a hairpin detector constructed and operative in accordance with a preferred embodiment of the present invention;

[0043] Fig. 5B is a simplified flowchart illustrating operation of a hairpin detector constructed and operative in accordance with a preferred embodiment of the present invention;

[0044] Fig. 6A is a simplified block diagram of a dicer-cut location detector constructed and operative in accordance with a preferred embodiment of the present invention;

[0045] Fig. 6B is a simplified flowchart illustrating training of a dicer-cut location detector constructed and operative in accordance with a preferred embodiment of the present invention;

[0046] Fig. 7A is a simplified block diagram of a target-gene binding-site detector constructed and operative in accordance with a preferred embodiment of the present invention;

- [0047] Fig. 7B is a simplified flowchart illustrating operation of a target-gene binding-site detector constructed and operative in accordance with a preferred embodiment of the present invention;
- [0048] Fig. 8 is a simplified flowchart illustrating operation of a function & utility analyzer constructed and operative in accordance with a preferred embodiment of the present invention;
- [0049] Fig. 9 is a simplified diagram describing a novel bioinformatically detected group of regulatory viral genes, referred to here as Viral Genomic Record (VGR) genes, each of which encodes an "operon-like" cluster of novel viral miRNA-like genes, which in turn modulates expression of a plurality of host target genes;
- [0050] Fig. 10 is a block diagram illustrating different utilities of genes of a novel group of genes, and operons of a novel group of operons, both of the present invention;
- [0051] Figs. 11A and 11B are simplified diagrams, which when taken together illustrate a mode of gene therapy applicable to genes of the novel group of genes of the present invention;
- [0052] Fig. 12A is an annotated sequence of EST72223 comprising novel gene GAM24 detected by the gene detection

system of the present invention;

[0053] Figs. 12B and 12C are pictures of laboratory results, which when taken together demonstrate laboratory confirmation of expression of the bioinformatically detected novel gene GAM24 of Fig. 12A;

[0054] Fig. 12D provides pictures of laboratory results, which when taken together demonstrate further laboratory confirmation of expression of the bioinformatically detected novel gene GAM24 of Fig. 12A;

[0055] Fig. 13A is an annotated sequence of an EST7929020 comprising novel genes GAM23 and GAM25 detected by the gene detection system of the present invention;

[0056] Fig. 13B is a picture of laboratory results, which confirm expression of bioinformatically detected novel genes GAM23 and GAM25 of Fig. 13A;

[0057] Fig. 13C is a picture of laboratory results, which confirm endogenous expression of bioinformatically detected novel gene GAM25 of Fig. 15A;

[0058] Fig. 14A is an annotated sequence of an EST1388749 comprising novel gene GAM26 detected by the gene detection system of the present invention;

[0059] Figs. 14B is a picture of laboratory results, which confirm expression of the bioinformatically detected novel gene

GAM26 of Fig. 14A;

[0060] Figs. 15A through 29D are schematic diagrams illustrating sequences, functions and utilities of 15 specific viral genes of the novel group of viral regulatory genes of the present invention, detected using the bioinformatic gene detection system described hereinabove with reference to Figs. 1 through 8 and

[0061] Figs. 30 through 31 are schematic diagrams illustrating sequences, functions and utilities of 2 specific viral genes of a group of novel regulatory "operon-like" viral genes of the present invention, detected using the bioinformatic gene detection system described hereinabove with reference to Figs. 1 through 9

BRIEF DESCRIPTION OF SEQUENCES

[0062] A Sequence Listing of genomic sequences of the present invention designated SEQ ID:1 through SEQ ID:406 is attached to this application, enclosed in computer readable form on CD-ROM. The genomic listing comprises the following nucleotide sequences: Genomic sequences designated SEQ ID:1 through SEQ ID:15 are nucleotide sequences of 15 gene precursors of respective novel genes of the present invention; Genomic sequences designated SEQ ID:16 through SEQ ID:30 are nucleotide sequences of

15 genes of the present invention; and Genomic sequences designated SEQ ID:31 through SEQ ID:406 are nucleotide sequences of 376 gene precursors of respective novel genes of the present invention.

DETAILED DESCRIPTION

[0063] Reference is now made to Fig. 1 which is a simplified diagram illustrating a mode by which genes of a novel group of viral genes of the present invention, modulate expression of known host target genes.

[0064] The novel genes of the present invention are viral micro RNA (miRNA)-like, regulatory RNA genes, modulating expression of known host target genes. This mode of modulation is common to other known miRNA genes, as described hereinabove with reference to the background of the invention section.

[0065] VGAM GENE is a viral gene contained in the virus genome and TARGET GENE is a human gene contained in the DNA of the human genome.

[0066] VGAM GENE encodes a VGAM PRECURSOR RNA. However, similar to other miRNA genes, and unlike most ordinary genes, its RNA, VGAM PRECURSOR RNA, does not encode a protein.

[0067] VGAM PRECURSOR RNA folds onto itself, forming VGAM

FOLDED PRECURSOR RNA. As Fig.1 illustrates, VGAM FOLDED PRECURSOR RNA forms a "hairpin structure" folding onto itself. As is well known in the art, this "hairpin structure" is typical genes of the miRNA genes, and is due to the fact that nucleotide sequence of the first half of the RNA of a gene in this group is an accurate or partial inversed-reversed sequence of the nucleotide sequence of its second half. By "inversed-reversed" is meant a sequence which is reversed and wherein each nucleotide is replaced by a complimentary nucleotide, as is well known in the art (e.g. ATGGC is the inversed-reversed sequence of GCCAT).

[0068] An enzyme complex, designated DICER COMPLEX, "dices" the VGAM FOLDED PRECURSOR RNA into a single stranded RNA segment, about 22 nucleotides long, designated VGAM RNA. As is known in the art, "dicing" of the hairpin structured RNA precursor into shorter RNA segments about 22 nucleotides long by a Dicer type enzyme is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins.

[0069] VGAM HOST TARGET GENE encodes a corresponding messenger RNA, designated VGAM HOST TARGET RNA. This VGAM HOST TARGET RNA comprises three regions: a 5"

untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR PROTEIN CODING and 3'UTR respectively.

- [0070] VGAM RNA binds complementarily a BINDING SITE, located on the 3'UTR segment of TARGET RNA. This complementarily binding is due to the fact that the nucleotide sequence of VGAM RNA is an accurate or partial inversed-reversed sequence of the nucleotide sequence of BINDING SITE.
- [0071] The complimentary binding of VGAM RNA to BINDING SITE inhibits translation of VGAM HOST TARGET RNA into VGAM HOST TARGET PROTEIN. VGAM HOST TARGET PROTEIN is therefore outlined by a broken line.
- [0072] It is appreciated by one skilled in the art that the mode of transcriptional inhibition illustrated by Fig. 1 with specific reference to VGAM genes of the present invention, is in fact common to all other miRNA genes. A specific complimentary binding site has been demonstrated only for Lin-4 and Let-7. All the other 93 newly discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complimentary binding, although specific complimentary binding sites for these genes have not yet been found (Ruvkun G., "Perspec-

tive: Glimpses of a tiny RNA world", Science 294 ,779 (2001)). The present invention discloses a novel group of viral genes, the VGAM genes, belonging to the miRNA genes group, and for which a specific and complimentary binding has been determined.

[0073] Reference is now made to Fig. 2 which is a simplified block diagram illustrating a bioinformatic gene detection system capable of detecting genes of the novel group of genes of the present invention, which system is constructed and operative in accordance with a preferred embodiment of the present invention.

[0074] A centerpiece of the present invention is a bioinformatic gene detection engine 100, which is a preferred implementation of a mechanism capable of bioinformatically detecting genes of the novel group of genes of the present invention.

[0075] The function of the bioinformatic gene detection engine 100 is as follows: it receives three types of input, expressed RNA data 102, sequenced DNA data 104, and protein function data 106, performs a complex process of analysis of this data as elaborated below, and based on this analysis produces output of a bioinformatically detected group of novel genes designated 108.

[0076] Expressed RNA data 102 comprises published expressed sequence tags (EST) data, , published mRNA data, as well as other sources of published RNA data. Sequenced DNA data 104 comprises alphanumeric data describing sequenced genomic data, which preferably includes annotation data such as location of known protein coding regions relative to the sequenced data. Protein function data 106 comprises scientific publications reporting studies which elucidated physiological function known proteins, and their connection, involvement and possible utility in treatment and diagnosis of various diseases. Expressed RNA data 102, sequenced DNA data 104 may preferably be obtained from data published by the National Center for Bioinformatics (NCBI) at the National Institute of Health (NIH), as well as from various other published data sources. Protein function data 106 may preferably be obtained from any one of numerous relevant published data sources, such as the Online Mendelian Inherited Disease In Man (OMIM) database developed by John Hopkins University, and also published by NCBI.

[0077] Prior to actual detection of bioinformatically detected novel genes 108 by the bioinformatic gene detection engine 100, a process of bioinformatic gene detection en-

gene training & validation designated 110 takes place.

This process uses the known miRNA genes as a training set (some 200 such genes have been found to date using biological laboratory means), to train the bioinformatic gene detection engine 100 to bioinformatically recognize miRNA-like genes, and their respective potential target binding sites. Bioinformatic gene detection engine training & validation 110 is further describe hereinbelow with reference to Fig. 3.

[0078] The bioinformatic gene detection engine 100 comprises several modules which are preferably activated sequentially, and are described as follows:

[0079] A non-coding genomic sequence detector 112 operative to bioinformatically detect non-protein coding genomic sequences. The non-coding genomic sequence detector 112 is further described hereinbelow with reference to Figs. 4A and 4B.

[0080] A hairpin detector 114 operative to bioinformatically detect genomic "hairpin-shaped" sequences, similar to VGAM FOLDED PRECURSOR of Fig. 1. The hairpin detector 114 is further described hereinbelow with reference to Figs. 5A and 5B.

[0081] A dicer-cut location detector 116 operative to bioinfor-

matically detect the location on a hairpin shaped sequence which is enzymatically cut by DICER COMPLEX of Fig. 1. The dicer-cut location detector 116 is further described hereinbelow with reference to Fig. 6A.

[0082] A target-gene binding-site detector 118 operative to bioinformatically detect host target having binding sites, the nucleotide sequence of which is partially complementary to that of a given genomic sequence, such as a sequence cut by DICER COMPLEX of Fig. 1. The target-gene binding-site detector 118 is further described hereinbelow with reference to Figs. 7A and 7B.

[0083] A function & utility analyzer 120 operative to analyze function and utility of host target, in order to identify host target which have a significant clinical function and utility. The function & utility analyzer 120 is further described hereinbelow with reference to Fig. 8.

[0084] Hardware implementation of the bioinformatic gene detection engine 100 is important, since significant computing power is preferably required in order to perform the computation of bioinformatic gene detection engine 100 in reasonable time and cost. As an example, it is estimated that using one powerful 8-processor PC Server, over 30 months of computing time (at 24 hours per day)

would be required in order to detect all miRNA genes in human EST data, and their respective binding sites.

[0085] For example, in order to address this challenge at reasonable time and cost, a preferred embodiment of the present invention may comprise a cluster of a large number of personal computers (PCs), such as 100 PCs (Pentium IV, 1.7GHz, with 40GB storage each), connected by Ethernet to several strong servers, such as 4 servers (2-CPU, Xeon 2.2GHz, with 200GB storage each), combined with an 8-processor server (8-CPU, Xeon 550Mhz w/ 8GB RAM) connected via 2 HBA fiber-channels to an EMC Clariion 100-disks, 3.6 Terabyte storage device. Additionally, preferably an efficient database computer program, such as Microsoft (TM) SQL-Server database computer program is used and is optimized to the specific requirements of bioinformatic gene detection engine 100. Furthermore, the PCs are preferably optimized to operate close to 100% CPU usage continuously, as is known in the art. Using suitable hardware and software may preferably reduce the required calculation time in the abovementioned example from 30 months to 20 days.

[0086] It is appreciated that the abovementioned hardware configuration is not meant to be limiting, and is given as an

illustration only. The present invention may be implemented in a wide variety of hardware and software configurations.

[0087] The present invention discloses 15 novel viral genes of the VGAM group of genes, which have been detected bioinformatically, as described hereinbelow with reference to Figs. 15 through 29. Laboratory confirmation of 4 genes of the GAM group of genes is described hereinbelow with reference to Figs. 12 through 14.

[0088] Reference is now made to Fig. 3 which is a simplified flowchart illustrating operation of a mechanism for training of a computer system to recognize the novel genes of the present invention. This mechanism is a preferred implementation of the bioinformatic gene detection engine training & validation 110 described hereinabove with reference to Fig. 2.

[0089] Bioinformatic gene detection engine training & validation 110 of Fig. 2 begins by training the bioinformatic gene detection engine to recognize known miRNA genes, as designated by numeral 122. This training step comprises hairpin detector training & validation 124, further described hereinbelow with reference to Fig. 12 A, dicer-cut location detector training & validation 126, further de-

scribed hereinbelow with reference to Fig. 6A and 6B, and target-gene binding-site detector training & validation 128, further described hereinbelow with reference to Fig. 7A.

[0090] Next, the bioinformatic gene detection engine 100 is used to bioinformatically detect sample novel genes, as designated by numeral 130. An example of a sample novel gene thus detected is described hereinbelow with reference to Fig. 12.

[0091] Finally, wet lab experiments are preferably conducted in order to validate expression and preferably function the sample novel genes detected by the bioinformatic gene detection engine 100 in the previous step. An example of wet-lab validation of the abovementioned sample novel gene bioinformatically detected by the system is described hereinbelow with reference to Figs. 13A and 13B.

[0092] Reference is now made to Fig. 4A which is a simplified block diagram of a preferred implementation of the non-coding genomic sequence detector 112 described hereinabove with reference to Fig. 2. Non-protein coding genomic sequence detector 112 of Fig. 2 preferably receives as input at least two types of published genomic data: expressed RNA data 102, including EST data and mRNA

data, and sequenced DNA data 104. After its initial training, indicated by numeral 134, and based on the above-mentioned input data, the non-protein coding genomic sequence detector 112 produces as output a plurality of non-protein coding genomic sequences 136. Preferred operation of the non-protein coding genomic sequence detector 112 is described hereinbelow with reference to Fig. 4B.

[0093] Reference is now made to Fig. 4B which is a simplified flowchart illustrating a preferred operation of the non-coding genomic sequence detector 112 of Fig. 2. Detection of non-protein coding genomic sequences to be further analyzed by the system generally preferably progresses in one of the following two paths.

[0094] A first path for detecting non-protein coding genomic sequences begins by receiving a plurality of known RNA sequences, such as EST data. Each RNA sequence is first compared to all known protein-coding sequences, in order to select only those RNA sequences which are non-protein coding. This can preferably be performed by BLAST comparison of the RNA sequence to known protein coding sequences. The abovementioned BLAST comparison to the DNA preferably also provides the localization of

the RNA on the DNA.

[0095] Optionally, an attempt may be made to "expend" the non-protein RNA sequences thus found, by searching for transcription start and end signals, upstream and downstream of location of the RNA on the DNA respectively, as is well known in the art.

[0096] A second path for detecting non-protein coding genomic sequences starts by receiving DNA sequences. The DNA sequences are parsed into non protein coding sequences, based on published DNA annotation data: extracting those DNA sequences which are between known protein coding sequences. Next, transcription start and end signals are sought. If such signals are found, and depending on their "strength", probable expressed non-protein coding genomic sequences are yielded.

[0097] Reference is now made to Fig. 5A which is a simplified block diagram of a preferred implementation of the hairpin detector 114 described hereinabove with reference to Fig. 2.

[0098] The goal of the hairpin detector 114 is to detect "hairpin" shaped genomic sequences, similar to those of known miRNA genes. As mentioned hereinabove with reference to Fig. 1, a "hairpin" genomic sequence refers to a ge-

nomie sequence which "folds onto itself" forming a hairpin like shape, due to the fact that nucleotide sequence of the first half of the nucleotide sequence is an accurate or

[0099] The hairpin detector 114 of Fig. 2 receives as input a plurality of non-protein coding genomic sequences 136 of Fig. 4A, and after a phase of hairpin detector training & validation 124 of Fig. 3, is operative to detect and output "hairpin shaped" sequences found in the input expressed non-protein coding sequences, designated by numeral 138.

[0100] The phase of hairpin detector training & validation 124 is an iterative process of applying the hairpin detector 114 to known hairpin shaped miRNA genes, calibrating the hairpin detector 114 such that it identifies the training set of known hairpins, as well as sequences which are similar thereto. Preferred operation of the hairpin detector 114 is described hereinbelow with reference to Fig. 5B.

[0101] Reference is now made to Fig. 5B which is a simplified flowchart illustrating a preferred operation of the hairpin detector 114 of Fig. 2.

[0102] A hairpin structure is a two dimensional folding structure, resulting from the nucleotide sequence pattern: the nucleotide sequence of the first half of the hairpin sequence

is an inversed-reversed sequence of the second half thereof. Different methodologies are known in the art for detection of various two dimensional and three dimensional hairpin structures.

[0103] In a preferred embodiment of the present invention, the hairpin detector 114 initially calculates possible 2-dimensional (2D) folding patterns of a given one of the non-protein coding genomic sequences 136, preferably using a 2D folding algorithm based on free-energy calculation, such as the Zucker algorithm, as is well known in the art.

[0104] Next, the hairpin detector 114 analyzes the results of the 2D folding, in order to determine the presence, and location of hairpin structures. A 2D folding algorithm typically provides as output a listing of the base-pairing of the 2D folded shape, i.e. a listing of which all two pairs of nucleotides in the sequence which will bond. The goal of this second step, is to assess this base-pairing listing, in order to determine if it describes a hairpin type bonding pattern.

[0105] The hairpin detector 114 then assess those hairpin structures found by the previous step, comparing them to hairpins of known miRNA genes, using various parameters

such as length, free-energy, amount and type of mismatches, etc. Only hairpins that bear statistically significant resemblance of the population of hairpins of known miRNAs, according to the abovementioned parameters are accepted.

[0106] Lastly, the hairpin detector 114 attempts to select those hairpin structures which are as stable as the hairpins of known miRNA genes. This may be achieved in various manners. A preferred embodiment of the present invention utilizes the following methodology comprising three steps:

[0107] First, the hairpin detector 114 attempts to group potential hairpins into "families" of closely related hairpins. As is known in the art, a free-energy calculation algorithm, typically provides multiple "versions" each describing a different possible 2D folding pattern for the given genomic sequence, and the free energy of such possible folding. The hairpin detector 114 therefore preferably assesses all hairpins found on all "versions", grouping hairpins which appear in different versions, but which share near identical locations into a common "family" of hairpins. For example, all hairpins in different versions, the center of which is within 7 nucleotides of each other may preferably

be grouped to a single "family".

[0108] Next, hairpin "families" are assessed, in order to select only those families which represent hairpins that are as stable as those of known miRNA hairpins. For example, preferably only families which are represented in at least 65% of the free-energy calculation 2D folding versions, are considered stable.

[0109] Finally, an attempt is made to select the most suitable hairpin from each selected family. For example, preferably the hairpin which appears in more versions than other hairpins, and in versions the free-energy of which is lower, may be selected.

[0110] Reference is now made to Fig. 6A which is a simplified block diagram of a preferred implementation of the dicer-cut location detector 116 described hereinabove with reference to Fig. 2.

[0111] The goal of the dicer-cut location detector 116 is to detect the location in which DICER COMPLEX of Fig. 1, comprising the enzyme Dicer, would "dice" the given hairpin sequence, similar to VGAM FOLDED PRECURSOR RNA, yielding VGAM RNA both of Fig. 1.

[0112] The dicer-cut location detector 116 of Fig. 2 therefore receives as input a plurality of hairpins on genomic se-

quences 138 of Fig. 5A, which were calculated by the previous step, and after a phase of dicer-cut location detector training & validation 126 of Fig. 3, is operative to detect a respective plurality of dicer-cut sequences from hairpins 140, one for each hairpin.

[0113] In a preferred embodiment of the present invention, the dicer-cut location detector 116 preferably uses a combination of neural networks, Bayesian networks, Markovian modeling, and Support Vector Machines (SVMs) trained on the known dicer-cut locations of known miRNA genes, in order to detect dicer-cut locations. Dicer-cut location detector training & validation 126, which is further described hereinbelow with reference to Fig. 6B.

[0114] Reference is now made to Fig. 6 B which is a simplified flowchart illustrating a preferred implementation of dicer-cut location detector training & validation 126 of Fig. 3. Dicer-cut location detector 116 first preprocesses known miRNA hairpins and their respective dicer-cut locations, so as to be able to properly analyze them and train the detection system accordingly:

[0115] The folding pattern is calculated for each known miRNA, preferably based on free-energy calculation, and the size of the hairpin, the size of the loop at the center of the

hairpin, and "bulges" (i.e. mismatched base-pairs) in the folded hairpin are noted.

[0116] The dicer-cut location, which is known for known miRNA genes, is noted relative to the above, as well as to the nucleotides in each location along the hairpin. Frequency of identity of nucleotides, and nucleotide-pairing, relative to their location in the hairpin, and relative to the known dicer-cut location in the known miRNA genes is analyzed and modeled.

[0117] Different techniques are well known in the art for analysis of existing pattern from a given "training set" of species belonging to a genus, which techniques are then capable, to a certain degree, to detect similar patterns in other species not belonging to the training-set genus. Such techniques include, but are not limited to neural networks, Bayesian networks, Support Vector Machines (SVM), Genetic Algorithms, Markovian modeling, and others, as is well known in the art.

[0118] Using such techniques, preferably a combination of several of the above techniques, the known hairpins are represented as a several different networks (such as neural, Bayesian, or SVM) input and output layers. Both nucleotide, and "bulge" (i.e. nucleotide pairing or mismatch)

are represented for each position in the hairpin, at the input layer, and a corresponding true/false flag at each position, indicating whether it was diced by dicer at the output layer. Multiple networks are preferably used concurrently, and the results therefrom are integrated and further optimized. Markovian modeling may also be used to validate the results and enhance their accuracy. Finally, the bioinformatic detection of dicer-cut location of a sample novel is confirmed by wet-lab experimentation.

[0119] Reference is now made to Fig. 7A which is a simplified block diagram of a preferred implementation of the target-gene binding-site detector 118 described hereinabove with reference to Fig. 2. The goal of the target-gene binding-site detector 118 is to detect a BINDING SITE of Fig. 1, located in an untranslated region of the RNA of a known gene, the nucleotide sequence of which BINDING SITE is at least partially complementary to that of a VGAM RNA of Fig. 1, thereby determining that the abovementioned known gene is a target gene of VGAM of Fig. 1.

[0120] The target-gene binding-site detector 118 of Fig. 2 therefore receives as input a plurality of dicer-cut sequences from hairpins 140 of Fig. 6A which were calcu-

lated by the previous step, and a plurality of potential target gene sequences 142 which derive sequence DNA data 104 of Fig. 2, and after a phase of target-gene binding-site detector training & validation 128 of Fig. 3, is operative to detect target-genes having binding site/s 144 the nucleotide sequence of which is at least partially complementary to that of each of the plurality of dicer-cut sequences from hairpins 140. Preferred operation of the target-gene binding-site detector is further described hereinbelow with reference to Fig. 7B.

[0121] Reference is now made to Fig. 7B which is a simplified flowchart illustrating a preferred operation of the target-gene binding-site detector 118 of Fig. 2. In a preferred embodiment of the present invention, the target-gene binding-site detector 118 first performs a BLAST comparison of the nucleotide sequence of each of the plurality of dicer-cut sequences from hairpins 140, to the potential target gene sequences 142, in order to find crude potential matches. Blast results are then filtered to results which are similar to those of known binding sites (e.g. binding sites of miRNA genes Lin-4 and Let-7 to target genes Lin-14, Lin-41, Lin 28 etc.). Next the binding site is expanded, checking if nucleotide sequenced immediately

adjacent to the binding site found by BLAST, may improve the match. Suitable binding sites, then are computed for free-energy and spatial structure. The results are analyzed, selecting only those binding sites, which have free-energy and spatial structure similar to that of known binding sites.

[0122] Reference is now made to Fig. 8 which is a simplified flowchart illustrating a preferred operation of the function & utility analyzer 120 described hereinabove with reference to Fig. 2. The goal of the function & utility analyzer 120 is to determine if a potential target gene is in fact a valid clinically useful target gene. Since a potential novel VGAM gene binding a binding site in the UTR of a target gene is understood to inhibit expression of that target gene, and if that target gene is shown to have a valid clinical utility, then in such a case it follows that the potential novel gene itself also has a valid useful function which is the opposite of that of the target gene.

[0123] The function & utility analyzer 120 preferably receives as input a plurality of potential novel target genes having binding-site/s 144, generated by the target-gene binding-site detector 118, both of Fig. 7A. Each potential gene, is evaluated as follows:

[0124] First the system first checks to see if the function of the potential target gene is scientifically well established. Preferably, this can be achieved bioinformatically by searching various published data sources presenting information on known function of proteins. Many such data sources exist and are published as is well known in the art.

[0125] Next, for those target genes the function of which is scientifically known and is well documented, the system then checks if scientific research data exists which links them to known diseases. For example, a preferred embodiment of the present invention utilizes the OMIM(TM) database published by NCBI, which summarizes research publications relating to genes which have been shown to be associated with diseases.

[0126] Finally, the specific possible utility of the target gene is evaluated. While this process too may be facilitated by bioinformatic means, it might require human evaluation of published scientific research regarding the target gene, in order to determine the utility of the target gene to the diagnosis and or treatment of specific disease. Only potential novel genes, the target-genes of which have passed all three examinations, are accepted as novel genes.

[0127] Reference is now made to Fig. 9, which is a simplified diagram describing a novel bioinformatically detected group of regulatory genes, referred to here as Viral Genomic Record (VGR) genes, that encode an "operon-like" cluster of novel viral miRNA-like genes, each modulating expression of a plurality of host target genes, the function and utility of which target genes is known.

[0128] VGR GENE (Viral Genomic Record Gene) is gene of a novel bioinformatically detected group of regulatory, non protein coding, RNA genes. The method by which VGR is detected is described hereinabove with reference to FIGS. 1-9.

[0129] VGR GENE encodes an RNA molecule, typically several hundred nucleotides long, designated VGR PRECURSOR RNA.

[0130] VGR PRECURSOR RNA folds spatially, as illustrated by VGR FOLDED PRECURSOR RNA, into a plurality of what is known in the art as "hairpin structures. The nucleotide sequence of VGR PRECURSOR RNA comprises a plurality of segments, the first half of each such segment having a nucleotide sequence which is at least a partial inversed-reversed sequence of the second half thereof, thereby causing formation of a plurality of "hairpin" structures, as is

well known in the art.

[0131] VGR FOLDED PRECURSOR RNA is naturally processed by cellular enzymatic activity, into 3 separate hairpin shaped RNA segments, each corresponding to VGAM FOLDED PRECURSOR RNA of Fig. 1, designated VGAM1 FOLDED PRECURSOR, VGAM2 FOLDED PRECURSOR and VGAM3 FOLDED PRECURSOR respectively.

[0132] The above mentioned VGAM precursors, are diced by DICER COMPLEX of FIG. 1, yielding short RNA segments of about 22 nucleotides in length, each corresponding to VGAM RNA of FIG. 1, designated VGAM1 RNA, VGAM2 RNA and VGAM3 RNA respectively.

[0133] VGAM1 RNA, VGAM2 RNA and VGAM3 RNA each bind complementarily to binding sites located in untranslated regions of respective host target, designated VGAM1-HOST TARGET RNA, VGAM2-HOST TARGET RNA and VGAM3-HOST TARGET RNA respectively. This binding inhibits translation of the respective target proteins designated VGAM1-HOST TARGET PROTEIN, VGAM2-HOST TARGET PROTEIN and VGAM3-HOST TARGET PROTEIN respectively.

[0134] The structure of VGAM genes comprised in a VGR GENE, and their mode of modulation of expression of their re-

spective target genes is described hereinabove with reference to Fig. 1. The bioinformatic approach to detection of VGAM genes comprised in a VGR GENE is described hereinabove with reference to Figs. 1 through 9.

[0135] The present invention discloses 17 novel viral genes of the VGR group of genes, which have been detected bioinformatically, as described hereinbelow with reference to Figs. 15 through 31. Laboratory confirmation of three genes of the VGR group of genes is described hereinbelow with reference to Figs. 12A through 14B.

[0136] In summary, the current invention discloses a very large number of novel viral VGR genes, each of which encodes a plurality of VGAM genes, which in turn may modulate expression of a plurality of host target proteins.

[0137] Reference is now made to Fig. 10 which is a block diagram illustrating different utilities of genes of the novel group of genes of the present invention referred to here as VGAM genes and VGR genes.

[0138] The present invention discloses a first plurality of novel genes referred to here as VGAM genes, and a second plurality of operon-like genes referred to here as VGR genes, each of the VGR genes encoding a plurality of VGAM genes. The present invention further discloses a very large

number of known target-genes, which are bound by, and the expression of which is modulated by each of the novel genes of the present invention. Published scientific data referenced by the present invention provides specific, substantial, and credible evidence that the abovementioned target genes modulated by novel genes of the present invention, are associated with various diseases. Specific novel genes of the present invention, target genes thereof and diseases associated therewith, are described hereinbelow with reference to Figs. 15 through 29. It is therefore appreciated that a function of VGAM genes and VGR genes of the present invention is modulation of expression of target genes related to known diseases, and that therefore utilities of novel genes of the present invention include diagnosis and treatment of the abovementioned diseases. Fig. 10 describes various types of diagnostic and therapeutic utilities of novel genes of the present invention.

[0139] A utility of novel genes of the present invention is detection of VGAM genes and of VGR genes. It is appreciated that since VGAM genes and VGR genes modulate expression of disease related target genes, that detection of expression of VGAM genes in clinical scenarios associated

with said diseases is a specific, substantial and credible utility. Diagnosis of novel genes of the present invention may preferably be implemented by RNA expression detection techniques, including but not limited to biochips, as is well known in the art. Diagnosis of expression of genes of the present invention may be useful for research purposes, in order to further understand the connection between the novel genes of the present invention and the abovementioned related diseases, for disease diagnosis and prevention purposes, and for monitoring disease progress.

[0140] Another utility of novel genes of the present invention is anti-VGAM gene therapy, a mode of therapy which allows up regulation of a disease related target-gene of a novel VGAM gene of the present invention, by lowering levels of the novel VGAM gene which naturally inhibits expression of that target gene. This mode of therapy is particularly useful with respect to target genes which have been shown to be under-expressed in association with a specific disease. Anti-VGAM gene therapy is further discussed hereinbelow with reference to Figs. 11A and 11B.

[0141] A further utility of novel genes of the present invention is VGAM replacement therapy, a mode of therapy which

achieves down regulation of a disease related target-gene of a novel VGAM gene of the present invention, by raising levels of the VGAM gene which naturally inhibits expression of that target gene. This mode of therapy is particularly useful with respect to target genes which have been shown to be over-expressed in association with a specific disease. VGAM replacement therapy involves introduction of supplementary VGAM gene products into a cell, or stimulation of a cell to produce excess VGAM gene products. VGAM replacement therapy may preferably be achieved by transfecting cells with an artificial DNA molecule encoding a VGAM gene, which causes the cells to produce the VGAM gene product, as is well known in the art.

[0142] Yet a further utility of novel genes of the present invention is modified VGAM therapy. Disease conditions are likely to exist, in which a mutation in a binding site of a VGAM gene prevents natural VGAM gene to effectively bind inhibit a disease related target-gene, causing up regulation of that target gene, and thereby contributing to the disease pathology. In such conditions, a modified VGAM gene is designed which effectively binds the mutated VGAM binding site, i.e. is an effective anti-sense of the

mutated VGAM binding site, and is introduced in disease effected cells. Modified VGAM therapy is preferably achieved by transfecting cells with an artificial DNA molecule encoding the modified VGAM gene, which causes the cells to produce the modified VGAM gene product, as is well known in the art.

[0143] An additional utility of novel genes of the present invention is induced cellular differentiation therapy. An aspect of the present invention is finding genes which determine cellular differentiation, as described hereinabove with reference to Fig. 11. Induced cellular differentiation therapy comprises transfection of cell with such VGAM genes thereby determining their differentiation as desired. It is appreciated that this approach may be widely applicable, inter alia as a means for auto transplantation harvesting cells of one cell-type from a patient, modifying their differentiation as desired, and then transplanting them back into the patient. It is further appreciated that this approach may also be utilized to modify cell differentiation in vivo, by transfecting cells in a genetically diseased tissue with a cell-differentiation determining VGAM gene, thus stimulating these cells to differentiate appropriately.

[0144] Reference is now made to Figs. 11A and 11B, simplified

diagrams which when taken together illustrate anti-VGAM gene therapy mentioned hereinabove with reference to Fig. 10. A utility of novel genes of the present invention is anti-VGAM gene therapy, a mode of therapy which allows up regulation of a disease related target-gene of a novel VGAM gene of the present invention, by lowering levels of the novel VGAM gene which naturally inhibits expression of that target gene. Fig. 11A shows a normal VGAM gene, inhibiting translation of a target gene of VGAM gene, by binding to a BINDING SITE found in an untranslated region of TARGET RNA, as described hereinabove with reference to Fig. 1.

[0145] Fig. 11B shows an example of anti-VGAM gene therapy. ANTI-VGAM RNA is short artificial RNA molecule the sequence of which is an anti-sense of VGAM RNA. Anti-VGAM treatment comprises transfecting diseased cells with ANTI-VGAM RNA, or with a DNA encoding thereof. The ANTI-VGAM RNA binds the natural VGAM RNA, thereby preventing binding of natural VGAM RNA to its BINDING SITE. This prevents natural translation inhibition of TARGET RNA by VGAM RNA, thereby up regulating expression of TARGET PROTEIN.

[0146] It is appreciated that anti-VGAM gene therapy is particu-

larly useful with respect to target genes which have been shown to be under-expressed in association with a specific disease.

[0147] Reference is now made to Fig. 12A which is an annotated sequence of an EST comprising a novel gene detected by the gene detection system of the present invention. Fig. 12A shows the nucleotide sequence of a known human non-protein coding EST (Expressed Sequence Tag), identified as EST72223. It is appreciated that the sequence of this EST comprises sequences of one known miRNA gene, identified as MIR98, and of one novel GAM gene, referred to here as GAM24, detected by the bioinformatic gene detection system of the present invention, described hereinabove with reference to Fig. 2.

[0148] Reference is now made to Figs. 12B and 12C that are pictures of laboratory results, which when taken together demonstrate laboratory confirmation of expression of the bioinformatically detected novel gene of Fig. 12A. Reference is now made to Fig. 12B which is a Northern blot analysis of MIR-98 and EST72223 transcripts. MIR-98 and EST72223 were reacted with MIR-98 and GAM24 probes as indicated in the figure. It is appreciated that the probes of both MIR-98 and GAM24 reacted with EST72223, indi-

cating that EST72223 contains the sequences of MIR-98 and of GAM24. It is further appreciated that the probe of GAM24 does not cross-react with MIR-98.

[0149] Reference is now made to Fig. 12C. A Northern blot analysis of EST72223 and MIR-98 transfections were performed, subsequently marking RNA by the MIR-98 and GAM24 probes . Left, Northern reacted with MIR-98, Right, Northern reacted with GAM24. The molecular Sizes of EST72223, MIR-98 and GAM24 are indicated by arrows. Hela are control cells that have not been introduced to exogenous RNA. EST and MIR-98 Transfections are RNA obtained from Hela transfected with EST72223 and MIR-98, respectively. MIR-98 and EST are the transcripts used for the transfection experiment. The results indicate that EST72223, when transfected into Hela cells, is cut yielding known miRNA gene MIR-98 and novel miRNA gene GAM24.

[0150] Reference is now made to Fig. 12D, which is a Northern blot of a lisate experiment with MIR-98 and GAM24. Northern blot analysis of hairpins in EST72223 . Left, Northern reacted with predicted Mir-98 hairpin probe, Right, Northern reacted with predicted GAM24 hairpin probe. The molecular size of EST Is indicated by arrow.

The molecular sizes of Mir-98 and GAM24 are 80nt and 100nt, respectively as indicated by arrows. The 22nt molecular marker is indicated by arrow. 1-Hela lysate; 2-EST incubated 4h with Hela lysate; 3-EST without lysate; 4-Mir transcript incubated 4h with Hela lysate; 5-Mir transcript incubated overnight with Hela lysate; 6- Mir transcript without lysate; 7-RNA extracted from Hela cells following transfection with Mir transcript.

[0151] Technical methods used in experiments, the results of which are depicted in Figs. 12B, 12C and 12D are as follows:

[0152] *Transcript preparations:* Digoxigenin (DIG) labeled transcripts were prepared from EST72223 (TIGER), MIR98 and predicted precursor hairpins by using a DIG RNA labeling kit (Roche Molecular Biochemicals) according to the manufacturer's protocol. Briefly, PCR products with T7 promoter at the 5' end or T3 promoter at the 3' end were prepared from each DNA in order to use it as a template to prepare sense and antisense transcripts, respectively. MIR-98 was amplified using EST72223 as a template with T7miR98 forward primer:

5'-"TAATACGACTCACTATAGGGTGAGGTAGTAAGTTGTATTGTT-3" and T3miR98 reverse primer:

5"-AATTAACCCTCACTAAAGGGAAAGTAGTAAGTTGTATAG
TT-3"EST72223 was amplified with T7-EST 72223 forward
primer:5"-TAATACGACTCACTATAGGCCCTTATTAGAGGAT
TCTGCT-3"and T3-EST72223 reverse
primer:5"-AATTAACCCTCACTAAAGGTTTTTTTTTCCTGAG
ACAGAGT-3" Bet-4 was amplified using EST72223 as a
templet with Bet-4 forward primer:
5"-GAGGCAGGAGAATTGCTTGA- 3" and T3-EST72223 re-
verse
primer:5"-AATTAACCCTCACTAAAGGCCTGAGACAGAGTCT
TGCTC-3"The PCR products were cleaned and used for
DIG-labeled or unlabeled transcription reactions with the
appropriate polymerase. For transfection experiments,
CAP reaction was performed by using a mMessage mMa-
chine kit (Ambion).

[0153] *Transfection procedure:* Transfection of Hela cells was per-
formed by using TransMessenger reagent (Qiagen) ac-
cording to the manufacture"s protocol. Briefly, Hela cells
were seeded to 1-2x 10⁶ cells per plate a day before
transfection. Two µg RNA transcripts were mixed with 8µl
Enhancer in a final volume of 100µl, mixed and incubated
at room temperature for 5 min. 16µl TransMessenger
reagent was added to the RNA-Enhancer, mixed and incu-

bated for additional 10 min. Cell plates were washed with sterile PBS twice and then incubated with the transfection mix diluted with 2.5 ml DMEM medium without serum. Cells were incubated with transfection mix for three hours under their normal growth condition (37°C and 5% CO₂) before the transfection mix was removed and a fresh DMEM medium containing serum was added to the cells. Cells were left to grow 48 hours before harvesting.

[0154] *Target RNA cleavage assay:* Cap-labeled target RNAs were generated using mMessage mMachineTM (Ambion). Caped RNA transcripts were preincubated at 30°C for 15 min in supplemented HeLa S100 obtained from Computer Cell Culture, Mos, Belgium. After addition of all components, final concentrations were 100mM target RNA, 1m M ATP, 0.2mM GTP, 10U/ml RNasin, 30µg/ml creatine kinase, 25mM creatine phosphate, and 50% S100 extract. Incubation was continued for 4 hours to overnight. Cleavage reaction was stopped by the addition of 8 volumes of proteinase K buffer (200mM Tris-HCl, pH 7.5, 25m M EDTA, 300mM NaCl, and 2% SDS). Proteinase K, dissolved in 50mM Tris-HCl, pH 8, 5m M CaCl₂, and 50% glycerol, was added to a final concentration of 0.6 mg/ml. Samples were subjected to phenol/chloroform extraction and kept

frozen until analyzed by urea-TBE PAGE.

[0155] *Northern analysis:* RNAs were extracted from cells by using Tri-reagent according to the manufacture's protocol. The RNAs were dissolved in water and heated to 65°C to disrupt any association of the 25nt RNA with larger RNA molecules. RNA were placed on ice and incubated for 30 min with PEG (MW=8000) in a final concentration of 5% and NaCl in a final concentration of 0.5M to precipitate high molecular weight nucleic acid. The RNAs were centrifuged at 10,000xg for 10 min to pellet the high molecular weight nucleic acid. The supernatant containing the low molecular weight RNAs was collected and three volumes of ethanol was added. The RNAs were placed at -20°C for at least two hours and then centrifuged at 10,000xg for 10 min. The pellets were dissolved in Urea-TBE buffer (1xTBE, 7M urea) for further analysis by a Northern blot.

[0156] RNA samples were boiled for 5 min before loading on 15%-8% polyacrylamide (19:1) gels containing 7M urea and 1xTBE. Gels were run in 1xTBE at a constant voltage of 300V and then transferred into a nylon membrane. The membrane was exposed to 3min ultraviolet light to cross link the RNAs to the membrane. Hybridization was per-

formed overnight with DIG-labeled probes at 42°C. Membranes were washed twice with SSCx2 and 0.2% SDS for 10 min. at 42°C and then washed twice with SSCx0.5 for 5 min at room temperature. The membrane was then developed by using a DIG luminescent detection kit (Roche) using anti DIG and CSPD reaction, according to the manufacturer's protocol.

[0157] It is appreciated that the data presented in Figs. 12A, 12B, 12C and 12D, when taken together validate the function of the bioinformatic gene detection engine 100 of Fig. 2. Fig. 12A shows a novel GAM gene bioinformatically detected by the bioinformatic gene detection engine 100, and Figs. 12B, 12C and 12D show laboratory confirmation of the expression of this novel gene. This is in accord with the engine training and validation methodology described hereinabove with reference to Fig. 3.

[0158] Reference is now made to Fig. 13A which is an annotated sequence of an EST comprising a novel gene detected by the gene detection system of the present invention. Fig. 13A shows the nucleotide sequence of a known human non-protein coding EST (Expressed Sequence Tag), identified as EST 7929020. It is appreciated that the sequence of this EST comprises sequences of two novel GAM genes,

referred to here as GAM23 and GAM25, detected by the bioinformatic gene detection system of the present invention, described hereinabove with reference to Fig. 2.

[0159] Reference is now made to Fig. 13B which presents pictures of laboratory results, that demonstrate laboratory confirmation of expression of the bioinformatically detected novel gene of Fig. 13A. Northern blot analysis of hairpins in EST7929020. Left, Northern reacted with predicted GAM25 hairpin probe, Right, Northern reacted with predicted GAM23 hairpin probe. The molecular size of EST is indicated by arrow. The molecular sizes of GAM23 and GAM25 are 60nt, as indicated by arrow. The 22nt molecular marker is indicated by arrow. 1-Hela lysate; 2- EST incubated 4h with Hela lysate ; 3- EST incubated overnight with Hela lysate; 4-EST without lysate; 5-GAM transcript; 6- GAM 22nt marker;7-GAM PCR probe; 8-RNA from control Hela cells; 9-RNA extracted from Hela cells following transfection with EST.

[0160] Reference is now made to Fig. 13C which is a picture of a Northern blot confirming Endogenous expression of bioinformatically detected gene GAM25 of Fig. 13A from in Hela cells. Northern was reacted with a predicted GAM25 hairpin probe. The molecular size of EST7929020

is indicated. The molecular sizes of GAM25 is 58nt, as indicated. A 19nt DNA oligo molecular marker is indicated. Endogenous expression of GAM25 in Hela total RNA fraction and in S-100 fraction is indicated by arrows.

1-GAM25 transcript; 2- GAM25 DNA oligo marker; 3-RNA from control Hela cells; 4-RNA extracted from Hela cells following transfection with EST; 5- RNA extracted from S-100 Hela lysate.

[0161] Reference is now made to Fig. 14A which is an annotated sequence of an EST comprising a novel gene detected by the gene detection system of the present invention. Fig. 14A shows the nucleotide sequence of a known human non-protein coding EST (Expressed Sequence Tag), identified as EST 1388749. It is appreciated that the sequence of this EST comprises sequence of a novel GAM gene, referred to here as GAM26, detected by the bioinformatic gene detection system of the present invention, described hereinabove with reference to Fig. 2.

[0162] Reference is now made to Fig. 14B which is a picture of Northern blot analysis, confirming expression of novel bioinformatically detected gene GAM26, and natural processing thereof from EST1388749. Northern reacted with predicted GAM26 hairpin probe. The molecular size of EST

is indicated by arrow. The molecular sizes of GAM26 is 130nt, as indicated by arrow. The 22nt molecular marker is indicated by arrow. 1–Hela lysate; 2–EST incubated 4h with Hela lysate; 3– EST incubated overnight with Hela lysate; 4–EST without lysate; 5–GAM transcript; 6– GAM 22nt marker; 7–GAM PCR probe.

[0163] Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 15 (VGAM15) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0164] VGAM15 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM15 was detected is described hereinabove with reference to Figs. 1–8.

[0165] VGAM15 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Immunodeficiency Virus 1. VGAM15 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0166] VGAM15 gene encodes a VGAM15 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM15 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM15 precursor RNA is designated SEQ ID:1, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:1 is located at position 7156 relative to the genome of Human Immunodeficiency Virus 1.

[0167] VGAM15 precursor RNA folds onto itself, forming VGAM15 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0168] An enzyme complex designated DICER COMPLEX, `dices` the VGAM15 folded precursor RNA into VGAM15 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 72%) nucleotide sequence of VGAM15 RNA is designated SEQ ID:16, and is provided hereinbelow with reference to the sequence listing part.

[0169] VGAM15 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM15 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM15 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[0170] VGAM15 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM15 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM15 RNA is an accurate or a partial inverted-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III

respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM15 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM15 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[0171] The complementary binding of VGAM15 RNA, herein designated VGAM RNA, to host target binding sites on VGAM15 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM15 host target RNA into VGAM15 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0172] It is appreciated that VGAM15 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM15 host target genes. The mRNA of each one of this plurality of VGAM15 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM15 RNA, herein designated VGAM RNA, and which when bound by VGAM15 RNA causes inhibition of translation of respective one or more VGAM15 host target proteins.

[0173] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM15 gene, herein designated VGAM GENE, on one or more VGAM15 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[0174] It is yet further appreciated that a function of VGAM15 is

inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM15 include diagnosis, prevention and treatment of viral infection by Human Immunodeficiency Virus 1. Specific functions, and accordingly utilities, of VGAM15 correlate with, and may be deduced from, the identity of the host target genes which VGAM15 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0175] Nucleotide sequences of the VGAM15 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM15 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM15 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM15 are further described hereinbelow with reference to Table 1.

[0176] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM15 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM15 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0177] As mentioned hereinabove with reference to Fig. 1, a function of VGAM15 gene, herein designated VGAM is inhibition of expression of VGAM15 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM15 correlate with, and may be deduced from, the identity of the target genes which VGAM15 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[0178] Primase, Polypeptide 2A, 58kDa (PRIM2A, Accession NM_000947) is a VGAM15 host target gene. PRIM2A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRIM2A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRIM2A BINDING SITE, designated SEQ ID:50, to the nucleotide sequence of VGAM15 RNA, herein designated VGAM RNA, also designated SEQ ID:16.

[0179] A function of VGAM15 is therefore inhibition of Primase, Polypeptide 2A, 58kDa (PRIM2A, Accession NM_000947). Accordingly, utilities of VGAM15 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRIM2A. RAP1B, Member of RAS Oncogene

Family (RAP1B, Accession NM_015646) is another VGAM15 host target gene. RAP1B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAP1B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAP1B BINDING SITE, designated SEQ ID:142, to the nucleotide sequence of VGAM15 RNA, herein designated VGAM RNA, also designated SEQ ID:16.

[0180] Another function of VGAM15 is therefore inhibition of RAP1B, Member of RAS Oncogene Family (RAP1B, Accession NM_015646), a gene which induces morphological reversion of a cell line transformed by a ras oncogene. Accordingly, utilities of VGAM15 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAP1B. The function of RAP1B has been established by previous studies. Three human cDNAs encoding 'new' RAS-related proteins, designated RAP1A, RAP1B, and RAP2, were isolated by Pizon et al. (1988). These proteins share approximately 50% amino acid identity with the classical RAS proteins and have numerous structural features in common. The most striking differ-

ence between the RAP and RAS proteins resides in their 61st amino acid: glutamine in RAS is replaced by threonine in RAP proteins. Animal model experiments lend further support to the function of RAP1B. Using mice transgenic for constitutive expression of Rap1a within the T cell lineage, Sebzda et al. (2002) found that instead of anergy, these T cells showed enhanced T cell receptor-mediated responses, both in thymocytes and in mature T cells. In addition, Rap1a activation induces strong activation of beta-1 (OMIM Ref. No. 135630) and beta-2 (OMIM Ref. No. 600065) integrins. The authors concluded that Rap1a positively influences T cells by augmenting their responses and directing integrin activation.

[0181] It is appreciated that the abovementioned animal model for RAP1B is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[0182] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0183] Pizon, V.; Chardin, P.; Lerosey, I.; Olofsson, B.; Tavitian, A. : Human cDNAs RAP1 and RAP2 homologous to the Drosophila gene Dras3 encode proteins closely related to

ras in the 'effector' region. Oncogene 3: 201–204, 1988. ;
and

[0184] Kitayama, H.; Sugimoto, Y.; Matsuzaki, T.; Ikawa, Y.; Noda, M. : A ras–related gene with transformation suppressor activity. Cell 56: 77–84, 1989. PubMed ID : 2642744 9.
Sebzda, E.; Brac.

[0185] Further studies establishing the function and utilities of RAP1B are found in John Hopkins OMIM database record ID 179530, and in cited publications numbered listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Ret Proto–oncogene (multiple endocrine neoplasia and medullary thyroid carcinoma 1, Hirschsprung disease) (RET, Accession NM_020629) is another VGAM15 host target gene. RET BINDING SITE1 through RET BINDING SITE4 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by RET, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RET BINDING SITE1 through RET BINDING SITE4, designated SEQ ID:173, SEQ ID:174, SEQ ID:179 and SEQ ID:37 respectively, to the nucleotide sequence of VGAM15 RNA, herein designated VGAM RNA,

also designated SEQ ID:16.

[0186] Another function of VGAM15 is therefore inhibition of Ret Proto-oncogene (multiple endocrine neoplasia and medullary thyroid carcinoma 1, Hirschsprung disease) (RET, Accession NM_020629), a gene which transduces signals for cell growth and differentiation. Accordingly, utilities of VGAM15 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RET. The function of RET has been established by previous studies. Using the approach of SSCP analysis established for all 20 exons of the RET gene, Seri et al. (1997) identified 7 additional mutations among 39 sporadic and familial cases of Hirschsprung disease (detection rate 18%). They considered that the relatively low efficiency of detecting mutations of RET in Hirschsprung patients cannot be accounted for by genetic heterogeneity, which is not supported by the results of linkage analysis in pedigrees analyzed to date. Almost 74% of the point mutations in their series, as well as in other patient series, were identified among long-segment patients, who represented only 25% of the patient population. Seri et al. (1997) found a C620R substitution in a patient affected with total colonic aganglionosis; the same mutation had

been found in medullary thyroid carcinoma. An R313Q mutation (164761.0026) was identified in homozygous state in a child born of consanguineous parents and was associated with the most severe Hirschsprung phenotype, namely, a total colonic aganglionosis with small bowel involvement. Eng (1996) reviewed the role of the RET protooncogene in multiple endocrine neoplasia type II and in Hirschsprung disease. Hoppener and Lips (1996) also reviewed RET gene mutations from the point of view of the molecular biology and the clinical aspects. Eng and Mulligan (1997) tabulated mutations of the RET gene in MEN2, the related sporadic tumors medullary thyroid carcinoma and pheochromocytoma, and familial and sporadic Hirschsprung disease. Germline mutations in 1 of 8 codons within RET cause the 3 subtypes of MEN2, namely, MEN2A, MEN2B, and familial medullary thyroid carcinoma. They stated that a somatic M918T mutation (164761.0013) accounts for the largest proportion of RET mutations detected in medullary thyroid carcinomas, most series showing a 30% to 50% range. It appeared that pheochromocytomas have a wider range of RET mutations. In contrast to MEN2, approximately 25% of patients with Hirschsprung disease have germline mutations scat-

tered throughout the length of RET.

[0187] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0188] Seri, M.; Yin, L.; Barone, A.; Bolino, A.; Celli, I.; Bocciardi, R.; Pasini, B.; Ceccherini, I.; Lerone, M.; Kristoffersson, U.; Larsson, L. T.; Casasa, J. M.; Cass, D. T.; Abramowicz, M. J.; Vanderwinden, J.-M.; Kravcenkiene, I.; Baric, I.; Silengo, M.; Martucciello, G.; Romeo, G. : Frequency of RET mutations in long- and short-segment Hirschsprung disease. Hum. Mutat. 9: 243-249, 1997. ; and

[0189] Hoppener, J. W. M.; Lips, C. J. M. : RET receptor tyrosine kinase gene mutations: molecular biological, physiological and clinical aspects. Europ. J. Clin. Invest. 26: 613-624, 1996.

[0190] Further studies establishing the function and utilities of RET are found in John Hopkins OMIM database record ID 164761, and in cited publications numbered 63-67, 71-70, 72-75, 517-166, 518-519, 189, 162-100, 587-105, 622-109, 173-112, 142-148, 520-155, 157, 161-160, 219-221, 62 and 224-230 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Diacylglycerol Kinase, Zeta 104kDa

(DGKZ, Accession NM_003646) is another VGAM15 host target gene. DGKZ BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DGKZ, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DGKZ BINDING SITE, designated SEQ ID:70, to the nucleotide sequence of VGAM15 RNA, herein designated VGAM RNA, also designated SEQ ID:16.

[0191] Another function of VGAM15 is therefore inhibition of Diacylglycerol Kinase, Zeta 104kDa (DGKZ, Accession NM_003646). Accordingly, utilities of VGAM15 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DGKZ. DKFZP586G1122 (Accession XM_028643) is another VGAM15 host target gene. DKFZP586G1122 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZP586G1122, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP586G1122 BINDING SITE, designated SEQ ID:265, to the nucleotide sequence of VGAM15 RNA, herein designated VGAM RNA,

also designated SEQ ID:16.

[0192] Another function of VGAM15 is therefore inhibition of DKFZP586G1122 (Accession XM_028643). Accordingly, utilities of VGAM15 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP586G1122. FLJ22127 (Accession NM_022775) is another VGAM15 host target gene. FLJ22127 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ22127, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22127 BINDING SITE, designated SEQ ID:192, to the nucleotide sequence of VGAM15 RNA, herein designated VGAM RNA, also designated SEQ ID:16.

[0193] Another function of VGAM15 is therefore inhibition of FLJ22127 (Accession NM_022775). Accordingly, utilities of VGAM15 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22127. LOC126248 (Accession XM_059007) is another VGAM15 host target gene. LOC126248 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC126248, corresponding to a HOST

TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC126248 BINDING SITE, designated SEQ ID:308, to the nucleotide sequence of VGAM15 RNA, herein designated VGAM RNA, also designated SEQ ID:16.

[0194] Another function of VGAM15 is therefore inhibition of LOC126248 (Accession XM_059007). Accordingly, utilities of VGAM15 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC126248. LOC146640 (Accession XM_085530) is another VGAM15 host target gene. LOC146640 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC146640, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146640 BINDING SITE, designated SEQ ID:323, to the nucleotide sequence of VGAM15 RNA, herein designated VGAM RNA, also designated SEQ ID:16.

[0195] Another function of VGAM15 is therefore inhibition of LOC146640 (Accession XM_085530). Accordingly, utilities of VGAM15 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC146640. LOC153416 (Accession XM_018473) is another VGAM15 host target gene. LOC153416 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC153416, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153416 BINDING SITE, designated SEQ ID:263, to the nucleotide sequence of VGAM15 RNA, herein designated VGAM RNA, also designated SEQ ID:16.

[0196] Another function of VGAM15 is therefore inhibition of LOC153416 (Accession XM_018473). Accordingly, utilities of VGAM15 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153416. LOC220790 (Accession XM_166037) is another VGAM15 host target gene. LOC220790 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC220790, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220790 BINDING SITE, designated SEQ ID:378, to

the nucleotide sequence of VGAM15 RNA, herein designated VGAM RNA, also designated SEQ ID:16.

[0197] Another function of VGAM15 is therefore inhibition of LOC220790 (Accession XM_166037). Accordingly, utilities of VGAM15 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220790. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 16 (VGAM16) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0198] VGAM16 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM16 was detected is described hereinabove with reference to Figs. 1–8.

[0199] VGAM16 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Immunodeficiency Virus 1. VGAM16 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0200] VGAM16 gene encodes a VGAM16 precursor RNA, herein

designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM16 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM16 precursor RNA is designated SEQ ID:2, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:2 is located at position 4668 relative to the genome of Human Immunodeficiency Virus 1.

[0201] VGAM16 precursor RNA folds onto itself, forming VGAM16 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0202] An enzyme complex designated DICER COMPLEX, `dices` the VGAM16 folded precursor RNA into VGAM16 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 79%) nucleotide sequence of VGAM16 RNA is designated SEQ ID:17, and is provided hereinbelow with reference to the sequence listing part.

[0203] VGAM16 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM16 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM16 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[0204] VGAM16 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM16 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM16 RNA is an accurate or a partial inverted-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, desig-

nated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM16 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM16 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[0205] The complementary binding of VGAM16 RNA, herein designated VGAM RNA, to host target binding sites on VGAM16 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM16 host target RNA into VGAM16 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0206] It is appreciated that VGAM16 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM16 host target genes. The mRNA of

each one of this plurality of VGAM16 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM16 RNA, herein designated VGAM RNA, and which when bound by VGAM16 RNA causes inhibition of translation of respective one or more VGAM16 host target proteins.

[0207] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM16 gene, herein designated VGAM GENE, on one or more VGAM16 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[0208] It is yet further appreciated that a function of VGAM16 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM16 include diagnosis, prevention and treatment of viral infection by Human Immunodeficiency Virus 1. Specific functions, and accordingly utilities, of VGAM16 correlate with, and may be deduced from, the identity of the host target genes which VGAM16 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0209] Nucleotide sequences of the VGAM16 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM16 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM16 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM16 are further described hereinbelow with reference to Table 1.

[0210] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM16 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM16 RNA, herein designated VGAM RNA, are described hereinbelow with refer-

ence to Table 2.

[0211] As mentioned hereinabove with reference to Fig. 1, a function of VGAM16 gene, herein designated VGAM is inhibition of expression of VGAM16 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM16 correlate with, and may be deduced from, the identity of the target genes which VGAM16 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[0212] Protein Kinase, CGMP-dependent, Type II (PRKG2, Accession NM_006259) is a VGAM16 host target gene. PRKG2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRKG2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRKG2 BINDING SITE, designated SEQ ID:103, to the nucleotide sequence of VGAM16 RNA, herein designated VGAM RNA, also designated SEQ ID:17.

[0213] A function of VGAM16 is therefore inhibition of Protein Kinase, CGMP-dependent, Type II (PRKG2, Accession NM_006259), a gene which regulate a great variety of functions, including smooth muscle relaxation, neuronal

excitability, and epithelial electrolyte transport. Accordingly, utilities of VGAM16 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRKG2. The function of PRKG2 has been established by previous studies. Nitric oxide (NO) and a broad spectrum of hormones, drugs, and toxins raise intracellular cGMP concentrations and thereby regulate a great variety of functions, including smooth muscle relaxation, neuronal excitability, and epithelial electrolyte transport. Pfeifer et al. (1996) noted that depending on the tissue, the increase in cGMP concentrations leads to the activation of different receptors, such as cyclic nucleotide phosphodiesterases. The identification of the physiologic mediator of cGMP is complicated by the existence of 2 forms of cGMP-dependent protein kinase (cGK), types I (see OMIM Ref. No. 176894) and II, which are encoded by distinct genes. Smooth muscle, platelets, and cerebellum contain high concentrations of cGK-I, whereas cGK-II is highly concentrated in brain, lung, and intestinal mucosa. The function of cGK-II is not well understood, although there is evidence that it mediates intestinal secretion of water and electrolytes induced by the E. coli toxin STa and the intestinal peptide guanylin (OMIM Ref. No. 139392).

To investigate the physiologic roles of cGK-II, Pfeifer et al. (1996) engineered a homozygous null mutation of the gene in mice by gene targeting. Mice deficient in cGK-II were resistant to E. coli STa and developed dwarfism that was caused by a severe defect in endochondral ossification at the growth plates. Membranous ossification was unaffected. Immunohistochemical staining showed a predominant expression of cGK-II in the late proliferative and early hypertrophic chondrocytes of the growth plate. Pfeifer et al. (1996) performed experiments with explanted bones from mutant and normal mice showing that the growth defect was intrinsic to the bone and not due to a general metabolic disturbance. The results indicated to the authors the central role played by cGK-II in diverse physiologic processes. Pfeifer et al. (1996) stated that identification of the pathway that mediates intestinal fluid secretion by E. coli STa has potential medical implications because STa causes traveler's diarrhea and about 50% of infant mortality in developing countries. Orstavik et al. (1996) cloned a human cDNA encoding type II cGK by using the mouse type II cGK cDNA to probe a cerebellum cDNA library. The 762-amino acid human type II cGK protein is 96% identical to the mouse and rat type II cGK pro-

teins. Human type II cGK is expressed as a 6-kb mRNA in prostate, small intestine, and colon and as a 4.4-kb mRNA in thymus and prostate. By PCR and Southern blotting of somatic cell hybrid panels, the authors mapped the human type II cGK gene to 4q13.1–q21.1.

[0214] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0215] Orstavik, S.; Solberg, R.; Tasken, K.; Nordahl, M.; Altherr, M. R.; Hansson, V.; Jahnsen, T.; Sandberg, M. : Molecular cloning, cDNA structure, and chromosomal localization of the human type II cGMP–dependent protein kinase. *Biochem. Biophys. Res. Commun.* 220: 759–765, 1996. ; and

[0216] Pfeifer, A.; Aszodi, A.; Seidler, U.; Ruth, P.; Hofmann, F.; Fassler, R. : Intestinal secretory defects and dwarfism in mice lacking cGMP–dependent protein kinase II. *Science* 274: 2082–.

[0217] Further studies establishing the function and utilities of PRKG2 are found in John Hopkins OMIM database record ID 601591, and in cited publications numbered 53–54 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. AFAP (Accession

NM_021638) is another VGAM16 host target gene. AFAP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AFAP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AFAP BINDING SITE, designated SEQ ID:183, to the nucleotide sequence of VGAM16 RNA, herein designated VGAM RNA, also designated SEQ ID:17.

[0218] Another function of VGAM16 is therefore inhibition of AFAP (Accession NM_021638). Accordingly, utilities of VGAM16 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AFAP. Complement Component 3a Receptor 1 (C3AR1, Accession NM_004054) is another VGAM16 host target gene. C3AR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C3AR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C3AR1 BINDING SITE, designated SEQ ID:76, to the nucleotide sequence of VGAM16 RNA, herein designated VGAM RNA, also designated SEQ ID:17.

[0219] Another function of VGAM16 is therefore inhibition of Complement Component 3a Receptor 1 (C3AR1, Accession NM_004054). Accordingly, utilities of VGAM16 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C3AR1. FLJ22029 (Accession NM_024949) is another VGAM16 host target gene. FLJ22029 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ22029, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22029 BINDING SITE, designated SEQ ID:203, to the nucleotide sequence of VGAM16 RNA, herein designated VGAM RNA, also designated SEQ ID:17.

[0220] Another function of VGAM16 is therefore inhibition of FLJ22029 (Accession NM_024949). Accordingly, utilities of VGAM16 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22029. Sema Domain, Seven Thrombospondin Repeats (type 1 and type 1-like), Transmembrane Domain (TM) and Short Cytoplasmic Domain, (semaphorin) 5A (SEMA5A, Accession NM_003966) is another VGAM16 host target gene. SEMA5A BINDING SITE is HOST TARGET binding site found

in the 3' untranslated region of mRNA encoded by SEMA5A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEMA5A BINDING SITE, designated SEQ ID:72, to the nucleotide sequence of VGAM16 RNA, herein designated VGAM RNA, also designated SEQ ID:17.

[0221] Another function of VGAM16 is therefore inhibition of Sema Domain, Seven Thrombospondin Repeats (type 1 and type 1-like), Transmembrane Domain (TM) and Short Cytoplasmic Domain, (semaphorin) 5A (SEMA5A, Accession NM_003966). Accordingly, utilities of VGAM16 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SEMA5A. Unc-5 Homolog D (C. elegans) (UNC5D, Accession NM_080872) is another VGAM16 host target gene. UNC5D BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UNC5D, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UNC5D BINDING SITE, designated SEQ ID:234, to the nucleotide sequence of VGAM16 RNA, herein designated VGAM RNA,

also designated SEQ ID:17.

[0222] Another function of VGAM16 is therefore inhibition of Unc-5 Homolog D (C. elegans) (UNC5D, Accession NM_080872). Accordingly, utilities of VGAM16 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UNC5D. LOC129446 (Accession XM_072203) is another VGAM16 host target gene. LOC129446 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC129446, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC129446 BINDING SITE, designated SEQ ID:315, to the nucleotide sequence of VGAM16 RNA, herein designated VGAM RNA, also designated SEQ ID:17.

[0223] Another function of VGAM16 is therefore inhibition of LOC129446 (Accession XM_072203). Accordingly, utilities of VGAM16 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC129446. LOC153396 (Accession XM_087662) is another VGAM16 host target gene. LOC153396 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC153396, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153396 BINDING SITE, designated SEQ ID:338, to the nucleotide sequence of VGAM16 RNA, herein designated VGAM RNA, also designated SEQ ID:17.

[0224] Another function of VGAM16 is therefore inhibition of LOC153396 (Accession XM_087662). Accordingly, utilities of VGAM16 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153396. LOC50999 (Accession NM_016040) is another VGAM16 host target gene. LOC50999 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC50999, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC50999 BINDING SITE, designated SEQ ID:145, to the nucleotide sequence of VGAM16 RNA, herein designated VGAM RNA, also designated SEQ ID:17.

[0225] Another function of VGAM16 is therefore inhibition of LOC50999 (Accession NM_016040). Accordingly, utilities

of VGAM16 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC50999. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 17 (VGAM17) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0226] VGAM17 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM17 was detected is described hereinabove with reference to Figs. 1–8.

[0227] VGAM17 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Immunodeficiency Virus 1. VGAM17 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0228] VGAM17 gene encodes a VGAM17 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM17 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide se–

quence of VGAM17 precursor RNA is designated SEQ ID:3, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:3 is located at position 5919 relative to the genome of Human Immunodeficiency Virus 1.

[0229] VGAM17 precursor RNA folds onto itself, forming VGAM17 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0230] An enzyme complex designated DICER COMPLEX, `dices` the VGAM17 folded precursor RNA into VGAM17 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 84%) nucleotide sequence of VGAM17 RNA is designated SEQ ID:18, and is

provided hereinbelow with reference to the sequence listing part.

[0231] VGAM17 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM17 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM17 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[0232] VGAM17 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM17 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM17 RNA is an accurate or a partial inverted-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM17 RNA,

herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM17 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[0233] The complementary binding of VGAM17 RNA, herein designated VGAM RNA, to host target binding sites on VGAM17 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM17 host target RNA into VGAM17 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0234] It is appreciated that VGAM17 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM17 host target genes. The mRNA of each one of this plurality of VGAM17 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM17 RNA, herein designated VGAM

RNA, and which when bound by VGAM17 RNA causes inhibition of translation of respective one or more VGAM17 host target proteins.

[0235] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM17 gene, herein designated VGAM GENE, on one or more VGAM17 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[0236] It is yet further appreciated that a function of VGAM17 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM17 include diagnosis, prevention and

treatment of viral infection by Human Immunodeficiency Virus 1. Specific functions, and accordingly utilities, of VGAM17 correlate with, and may be deduced from, the identity of the host target genes which VGAM17 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0237] Nucleotide sequences of the VGAM17 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM17 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM17 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM17 are further described hereinbelow with reference to Table 1.

[0238] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM17 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM17 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0239] As mentioned hereinabove with reference to Fig. 1, a function of VGAM17 gene, herein designated VGAM is inhibition of expression of VGAM17 target genes. It is ap-

preciated that specific functions, and accordingly utilities, of VGAM17 correlate with, and may be deduced from, the identity of the target genes which VGAM17 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[0240] KIAA0830 (Accession XM_045759) is a VGAM17 host target gene. KIAA0830 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0830, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0830 BINDING SITE, designated SEQ ID:290, to the nucleotide sequence of VGAM17 RNA, herein designated VGAM RNA, also designated SEQ ID:18.

[0241] A function of VGAM17 is therefore inhibition of KIAA0830 (Accession XM_045759). Accordingly, utilities of VGAM17 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0830. Preimplantation Protein 3 (PREI3, Accession XM_038960) is another VGAM17 host target gene. PREI3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PREI3, corresponding to a

HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PREI3 BINDING SITE, designated SEQ ID:275, to the nucleotide sequence of VGAM17 RNA, herein designated VGAM RNA, also designated SEQ ID:18.

[0242] Another function of VGAM17 is therefore inhibition of Preimplantation Protein 3 (PREI3, Accession XM_038960). Accordingly, utilities of VGAM17 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PREI3. SEC15L (Accession XM_051147) is another VGAM17 host target gene. SEC15L BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SEC15L, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEC15L BINDING SITE, designated SEQ ID:297, to the nucleotide sequence of VGAM17 RNA, herein designated VGAM RNA, also designated SEQ ID:18.

[0243] Another function of VGAM17 is therefore inhibition of SEC15L (Accession XM_051147). Accordingly, utilities of VGAM17 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with SEC15L. LOC152317 (Accession XM_098189) is another VGAM17 host target gene. LOC152317 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152317, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152317 BINDING SITE, designated SEQ ID:352, to the nucleotide sequence of VGAM17 RNA, herein designated VGAM RNA, also designated SEQ ID:18.

[0244] Another function of VGAM17 is therefore inhibition of LOC152317 (Accession XM_098189). Accordingly, utilities of VGAM17 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152317. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 18 (VGAM18) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0245] VGAM18 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM18 was detected is described hereinabove with reference to Figs. 1–8.

[0246] VGAM18 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Immunodeficiency Virus 1. VGAM18 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0247] VGAM18 gene encodes a VGAM18 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM18 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM18 precursor RNA is designated SEQ ID:4, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:4 is located at position 1459 relative to the genome of Human Immunodeficiency Virus 1.

[0248] VGAM18 precursor RNA folds onto itself, forming VGAM18 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is

due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0249] An enzyme complex designated DICER COMPLEX, `dices` the VGAM18 folded precursor RNA into VGAM18 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 72%) nucleotide sequence of VGAM18 RNA is designated SEQ ID:19, and is provided hereinbelow with reference to the sequence listing part.

[0250] VGAM18 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM18 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM18 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[0251] VGAM18 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM18 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM18 RNA is an accurate or a partial inverted-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM18 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM18 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[0252] The complementary binding of VGAM18 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM18 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM18 host target RNA into VGAM18 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0253] It is appreciated that VGAM18 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM18 host target genes. The mRNA of each one of this plurality of VGAM18 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM18 RNA, herein designated VGAM RNA, and which when bound by VGAM18 RNA causes inhibition of translation of respective one or more VGAM18 host target proteins.

[0254] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM18 gene, herein designated VGAM GENE, on one or more VGAM18 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with

reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[0255] It is yet further appreciated that a function of VGAM18 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM18 include diagnosis, prevention and treatment of viral infection by Human Immunodeficiency Virus 1. Specific functions, and accordingly utilities, of VGAM18 correlate with, and may be deduced from, the identity of the host target genes which VGAM18 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0256] Nucleotide sequences of the VGAM18 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM18 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of

VGAM18 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM18 are further described hereinbelow with reference to Table 1.

[0257] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM18 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM18 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0258] As mentioned hereinabove with reference to Fig. 1, a function of VGAM18 gene, herein designated VGAM is inhibition of expression of VGAM18 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM18 correlate with, and may be deduced from, the identity of the target genes which VGAM18 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[0259] Down Syndrome Critical Region Gene 1 (DSCR1, Accession NM_004414) is a VGAM18 host target gene. DSCR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DSCR1, corresponding to a HOST TARGET binding site such as BINDING

SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DSCR1 BINDING SITE, designated SEQ ID:81, to the nucleotide sequence of VGAM18 RNA, herein designated VGAM RNA, also designated SEQ ID:19.

[0260] A function of VGAM18 is therefore inhibition of Down Syndrome Critical Region Gene 1 (DSCR1, Accession NM_004414), a gene which inhibits calcineurin-dependent transcriptional responses. Accordingly, utilities of VGAM18 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DSCR1. The function of DSCR1 has been established by previous studies. The study of patients with partial trisomy 21 has defined an area of approximately 3 Mb at chromosomal region 21q22 as the minimal candidate region for the Down syndrome phenotype (OMIM Ref. No. 190685). Using a novel exon cloning strategy, Fuentes et al. (1995) identified several putative exons from region 21q22.1-q22.2. One exon was used to isolate fetal brain cDNAs corresponding to a gene that the authors designated DSCR1. The predicted 171-amino acid protein contains 2 proline-rich regions, a putative DNA-binding domain, and an acidic region. Northern blot analysis re-

vealed that the 2.2-kb DSCR1 transcript is expressed at the highest levels in fetal brain and adult heart and at lower levels in various other tissues. An additional 2-kb mRNA was detected in fetal and adult liver. Increased expression in the brains of young rats compared with adults suggested to Fuentes et al. (1995) that DSCR1 plays a role during central nervous system development. Fuentes et al. (1997) determined that DSCR1 spans nearly 45 kb and contains 7 exons, 4 of which are alternative first exons. They found tissue-specific expression patterns for the alternative transcripts. Kingsbury and Cunningham (2000) referred to the proteins encoded by the MCIP genes as calciressins. Functional analysis showed that when expressed in yeast, DSCR1 and ZAKI4 inhibited calcineurin function. The authors proposed that increased expression of DSCR1 in trisomy-21 individuals may contribute to the neurologic, cardiac, or immunologic defects of Down syndrome.

[0261] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0262] Fuentes, J. J.; Pritchard, M. A.; Estivill, X. : Genomic organization, alternative splicing, and expression patterns of

the DSCR1 (Down syndrome candidate region 1) gene. Genomics 44: 358–361, 1997. ; and

[0263] Kingsbury, T. J.; Cunningham, K. W. : A conserved family of calcineurin regulators. Genes Dev. 14: 1595–1604, 2000.

[0264] Further studies establishing the function and utilities of DSCR1 are found in John Hopkins OMIM database record ID 602917, and in cited publications numbered 269, 274–27 and 251–252 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Engulfment and Cell Motility 2 (ced-12 homolog, C. elegans) (ELMO2, Accession NM_133171) is another VGAM18 host target gene. ELMO2 BINDING SITE1 and ELMO2 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ELMO2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ELMO2 BINDING SITE1 and ELMO2 BINDING SITE2, designated SEQ ID:235 and SEQ ID:186 respectively, to the nucleotide sequence of VGAM18 RNA, herein designated VGAM RNA, also designated SEQ ID:19.

[0265] Another function of VGAM18 is therefore inhibition of En-

gulfment and Cell Motility 2 (ced-12 homolog, *C. elegans*) (ELMO2, Accession NM_133171). Accordingly, utilities of VGAM18 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ELMO2. Fibroblast Growth Factor 5 (FGF5, Accession NM_004464) is another VGAM18 host target gene. FGF5 BINDING SITE1 and FGF5 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by FGF5, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FGF5 BINDING SITE1 and FGF5 BINDING SITE2, designated SEQ ID:83 and SEQ ID:180 respectively, to the nucleotide sequence of VGAM18 RNA, herein designated VGAM RNA, also designated SEQ ID:19.

[0266] Another function of VGAM18 is therefore inhibition of Fibroblast Growth Factor 5 (FGF5, Accession NM_004464), a gene which induces transformation and may regulate neuronal differentiation. Accordingly, utilities of VGAM18 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FGF5. The function of FGF5 has been established by previous studies. Zhan et al. (1988) identified a fifth oncogene related to fibroblast

growth factors and termed it FGF5. The other four are FGFA (OMIM Ref. No. 131220), FGFB (OMIM Ref. No. 134920), INT2 (OMIM Ref. No. 164950), and HST (OMIM Ref. No. 164980). FGF5 was discovered when it acquired transforming potential by a DNA rearrangement accompanying transfection of NIH 3T3 cells with human tumor DNA. Two regions of the FGF5 sequence, containing 122 of its 267 amino acid residues, were 40 to 50% homologous to the sequences of the 4 other members of the FGF oncogene family. FGF5, furthermore, was found to have a 3-exon structure typical for members of this family. FGF5 was found to be expressed in neonatal brain and in 3 of 13 human tumor cell lines examined. Nguyen et al. (1988) mapped FGF5 to 4q21 by in situ hybridization. Thus, it is not in the same cluster as the related HST and INT2 genes, which are coamplified in some tumor cells and were found by Nguyen et al. (1988), using pulsed field gel analysis, to be separated by only 40 kb. By polymerase chain reaction (PCR) amplification of target sequences in DNAs from somatic cell hybrids, Dionne et al. (1990) mapped the FGF5 gene to chromosome 4. By in situ chromosomal hybridization, Mattei et al. (1992) demonstrated that the corresponding gene in the mouse is on chromosome 5.

Hebert et al. (1994) found that mice homozygous for a null allele of the *Fgf5* gene, produced by gene targeting in embryonic stem cells, have abnormally long hair. This phenotype appeared identical to that of mice homozygous for the spontaneous mutation 'angora' (*go*). The transgenic mutant and the '*go*' mutant failed to complement one another, and exon 1 of *Fgf5* was found to be deleted in DNA from *go* homozygotes. Expression of *Fgf5* is detected in hair follicles from wildtype mice and is localized to the outer root sheath during the anagen VI phase of the hair growth cycle. The findings were interpreted as evidence that FGF5 functions as an inhibitor of hair elongation, thus identifying a molecule whose normal function is apparently to regulate one step in the progression of the follicle through the hair growth cycle. It will be of interest to search for mutations in the FGF5 gene in hypertrichosis universalis (145700, 145701) as well as in other forms of hypertrichosis such as hairy elbows (OMIM Ref. No. 139600).

[0267] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0268] Zhan, X.; Bates, B.; Hu, X.; Goldfarb, M. : The human FGF-

5 oncogene encodes a novel protein related to fibroblast growth factors. Molec. Cell. Biol. 8: 3487–3495, 1988. ; and

[0269] Hebert, J. M.; Rosenquist, T.; Gotz, J.; Martin, G. R. : FGF5 as a regulator of the hair growth cycle: evidence from targeted and spontaneous mutations. Cell 78: 1017–1025, 1994.

[0270] Further studies establishing the function and utilities of FGF5 are found in John Hopkins OMIM database record ID 165190, and in cited publications numbered 17–18, and 19–20 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Protein Kinase, Y-linked (PRKY, Accession NM_002760) is another VGAM18 host target gene. PRKY BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRKY, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRKY BINDING SITE, designated SEQ ID:62, to the nucleotide sequence of VGAM18 RNA, herein designated VGAM RNA, also designated SEQ ID:19.

[0271] Another function of VGAM18 is therefore inhibition of

Protein Kinase, Y-linked (PRKY, Accession NM_002760), a gene which is a putative protein kinase. Accordingly, utilities of VGAM18 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRKY. The function of PRKY has been established by previous studies. PRKX (OMIM Ref. No. 300083) is a novel serine/threonine subtype of protein kinase that appears to encode a protein related to the catalytic subunit of the cAMP-dependent protein kinases, which are key players in the cellular responses to the second messenger cAMP. Klink et al. (1995) found that somatic cell hybrid analysis of PRKX under high stringency conditions revealed at least 3 further loci closely related to this gene in the human, constituting a small subfamily. Schiebel et al. (1997) isolated and characterized the PRKY gene, which is highly homologous to the PRKX gene on Xp22.3 and represents a member of the cAMP-dependent serine/threonine protein kinase gene family. Abnormal interchange can occur anywhere between Xp and Yp proximal to SRY (OMIM Ref. No. 480000). Schiebel et al. (1997) demonstrated that abnormal interchange in XX males (OMIM Ref. No. 278850) and XY females (OMIM Ref. No. 306100) happens particularly frequently between PRKX and PRKY. In a collection of 26

XX males and 4 XY females, between 27 and 35% of the interchanges took place between PRK homologs, but at different sites within the gene. PRKY and PRKX are located far from the pseudoautosomal region, where XY exchange normally takes place. Schiebel et al. (1997) stated that the unprecedented high sequence identity and identical orientation of PRKY to its homologous partner on the X chromosome, PRKX, explains the high frequency of abnormal pairing and the subsequent ectopic recombination, leading to XX males and XY females and to the highest rate of recombination outside the pseudoautosomal region.

Schiebel et al. (1997) used FISH analysis to map the PRKY gene to Yp11.2 in close proximity to AMELY (OMIM Ref. No. 410000); the autosomal copy, a pseudogene (OMIM Ref. No. PRKXP1), to 15q26; and a further X-linked pseudogene (OMIM Ref. No. PRKXP2) to Xq12-q13.

[0272] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0273] Schiebel, K.; Mertz, A.; Winkelmann, B.; Glaser, B.; Schempp, W.; Rappold, G. : FISH localization of the human Y-homolog of protein kinase PRKX (PRKY) to Yp11.2 and two pseudogenes to 15q26 and Xq12-q13. Cytogenet.

Cell Genet. 76: 49–52, 1997. ; and

[0274] Schiebel, K.; Winkelmann, M.; Mertz, A.; Xu, X.; Page, D. C.; Weil, D.; Petit, C.; Rappold, G. A. : Abnormal XY interchange between a novel isolated protein kinase gene, PRKY, and its h.

[0275] Further studies establishing the function and utilities of PRKY are found in John Hopkins OMIM database record ID 400008, and in cited publications numbered 523–52 and 460 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Ring Finger Protein 18 (RNF18, Accession NM_020358) is another VGAM18 host target gene. RNF18 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by RNF18, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RNF18 BINDING SITE, designated SEQ ID:172, to the nucleotide sequence of VGAM18 RNA, herein designated VGAM RNA, also designated SEQ ID:19.

[0276] Another function of VGAM18 is therefore inhibition of Ring Finger Protein 18 (RNF18, Accession NM_020358). Accordingly, utilities of VGAM18 include diagnosis, pre-

vention and treatment of diseases and clinical conditions associated with RNF18. Solute Carrier Family 1 (glial high affinity glutamate transporter), Member 3 (SLC1A3, Accession NM_004172) is another VGAM18 host target gene. SLC1A3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC1A3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC1A3 BINDING SITE, designated SEQ ID:77, to the nucleotide sequence of VGAM18 RNA, herein designated VGAM RNA, also designated SEQ ID:19.

[0277] Another function of VGAM18 is therefore inhibition of Solute Carrier Family 1 (glial high affinity glutamate transporter), Member 3 (SLC1A3, Accession NM_004172), a gene which is a transporter molecule that regulates neurotransmitter concentrations at excitatory synapses of the mammalian CNS. Accordingly, utilities of VGAM18 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC1A3. The function of SLC1A3 has been established by previous studies.

Kirschner et al. (1994) mapped the human EAAT1 gene to 5p13 by fluorescence in situ hybridization. They used in-

terspecific backcross analysis to map the murine homolog to chromosome 15 in a region of homology to human 5p13. They commented that the EAAT1 locus may be related to the syndrome of microcephaly and mental retardation observed by Keppen et al. (1992) in association with interstitial deletion of distal band 5p13. In the retina, the glutamate transporter GLAST is expressed in Muller cells, whereas the glutamate transporter GLT1 is found only in cones and various types of bipolar cells. To investigate the functional role of this differential distribution of glutamate transporters, Harada et al. (1998) analyzed Glast and Glt1 mutant mice. In Glast-deficient mice, the electroretinogram b-wave and oscillatory potentials were reduced and retinal damage after ischemia was exacerbated, whereas Glt1-deficient mice showed almost normal electroretinograms and mildly increased retinal damage after ischemia. These results demonstrated that Glast is required for normal signal transmission between photoreceptors and bipolar cells and that both Glast and Glt1 play a neuroprotective role during ischemia in the retina.

[0278] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0279] Kirschner, M. A.; Arriza, J. L.; Copeland, N. G.; Gilbert, D. J.; Jenkins, N. A.; Magenis, E.; Amara, S. G. : The mouse and human excitatory amino acid transporter gene (EAAT1) maps to mouse chromosome 15 and a region of syntenic homology on human chromosome 5. *Genomics* 22: 631–633, 1994. ; and

[0280] Harada, T.; Harada, C.; Watanabe, M.; Inoue, Y.; Sakagawa, T.; Nakayama, N.; Sasaki, S.; Okuyama, S.; Watase, K.; Wada, K.; Tanaka, K. : Functions of the two glutamate transporters GLAST a.

[0281] Further studies establishing the function and utilities of SLC1A3 are found in John Hopkins OMIM database record ID 600111, and in cited publications numbered 81–87 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Vitelliform Macular Dystrophy (Best disease, bestrophin) (VMD2, Accession NM_004183) is another VGAM18 host target gene. VMD2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by VMD2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of VMD2 BINDING SITE, designated SEQ ID:78, to the nu–

cleotide sequence of VGAM18 RNA, herein designated VGAM RNA, also designated SEQ ID:19.

[0282] Another function of VGAM18 is therefore inhibition of Vitelliform Macular Dystrophy (Best disease, bestrophin) (VMD2, Accession NM_004183), a gene which is a chloride channel. Accordingly, utilities of VGAM18 include diagnosis, prevention and treatment of diseases and clinical conditions associated with VMD2. The function of VMD2 has been established by previous studies. Petrukhin et al. (1998) found that the VMD2 cDNA encodes a 585-amino acid protein with a mass of 68 kD and an isoelectric point of 6.9. The hydropathy profile predicted the presence of at least 4 putative transmembrane domains. Alternatively, these stretches of hydrophobic amino acids may be involved in the formation of hydrophobic pockets or may interact tightly with the membrane without crossing it. A mouse VMD2 probe representing a protein fragment with 89% identity to human VMD2 demonstrated exquisitely specific expression in the retinal pigment epithelium (RPE) of the adult mouse eye; similar results were seen in the human retina. The only other site of VMD2 gene expression identified by in situ hybridization was Sertoli cells in mouse testis. Petrukhin et al. (1998) proposed the name

'bestrophin' for the protein encoded by the VMD2 gene. Using heterologous expression, Sun et al. (2002) showed that the human, *Drosophila*, and *C. elegans* bestrophin homologs form oligomeric chloride channels, and that human bestrophin is sensitive to intracellular calcium. Each of 15 missense mutations associated with vitelliform macular dystrophy greatly reduced or abolished the membrane current. Four of these mutant bestrophins were co-expressed with wildtype and each dominantly inhibited the wildtype membrane current, consistent with the dominant nature of the disorder. These experiments established the existence of a new chloride channel family and VMD as a channelopathy.

[0283] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0284] Petrukhin, K.; Koisti, M. J.; Bakall, B.; Li, W.; Xie, G.; Marknell, T.; Sandgren, O.; Forsman, K.; Holmgren, G.; Andreasson, S.; Vujic, M.; Bergen, A. A. B.; McGarty-Dugan, V.; Figueroa, D.; Austin, C. P.; Metzker, M. L.; Caskey, C. T.; Wadelius, C. : Identification of the gene responsible for Best macular dystrophy. *Nature Genet.* 19: 241-247, 1998. ; and

[0285] Sun, H.; Tsunenari, T.; Yau, K.-W.; Nathans, J. : The vitelliform macular dystrophy protein defines a new family of chloride channels. *Proc. Nat. Acad. Sci.* 99: 4008–4013, 2002.

[0286] Further studies establishing the function and utilities of VMD2 are found in John Hopkins OMIM database record ID 153700, and in cited publications numbered 113–129, 129–13 and 563–586 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. X-ray Repair Complementing Defective Repair In Chinese Hamster Cells 3 (XRCC3, Accession NM_005432) is another VGAM18 host target gene. XRCC3 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by XRCC3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of XRCC3 BINDING SITE, designated SEQ ID:91, to the nucleotide sequence of VGAM18 RNA, herein designated VGAM RNA, also designated SEQ ID:19.

[0287] Another function of VGAM18 is therefore inhibition of X-ray Repair Complementing Defective Repair In Chinese Hamster Cells 3 (XRCC3, Accession NM_005432), a gene

which is required for meiotic recombination, synaptonemal complex formation and cell cycle progression. Accordingly, utilities of VGAM18 include diagnosis, prevention and treatment of diseases and clinical conditions associated with XRCC3. The function of XRCC3 has been established by previous studies. Masson et al. (2001) found that antibody directed against RAD51C (OMIM Ref. No. 602774) coimmunoprecipitated XRCC2 in an endogenous complex with RAD51C in HeLa cell lysates. Gel filtration of the complex suggested that a heterodimer is formed between the proteins. Using coprecipitation and multiple pull-down assays, Liu et al. (2002) confirmed interaction between these proteins. They also found that RAD51 coprecipitates with XRCC3, suggesting that RAD51 can be present in a trimeric complex of XRCC3, RAD51C, and RAD51. Brenneman et al. (2002) found that XRCC3 mutant cells displayed radically altered homologous recombination (HR) product spectra, with increased gene conversion tract lengths, increased frequencies of discontinuous tracts, and frequent local rearrangements associated with HR. These results indicated that XRCC3 function is not limited to HR initiation, but extends to later stages in formation and resolution of HR intermediates, possibly by

stabilizing heteroduplex DNA. The results further demonstrated that HR defects can promote genomic instability not only through failure to initiate HR (leading to nonhomologous repair), but also through aberrant processing of HR intermediates. The authors suggested that both mechanisms may contribute to carcinogenesis in HR-deficient cells.

[0288] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0289] Masson, J.-Y.; Tarsounas, M. C.; Stasiak, A. Z.; Stasiak, A.; Shah, R.; McIlwraith, M. J.; Benson, F. E.; West, S. C. : Identification and purification of two distinct complexes containing the five RAD51 paralogs. *Genes Dev.* 15: 3296–3307, 2001. ; and

[0290] Brenneman, M. A.; Wagener, B. M.; Miller, C. A.; Allen, C.; Nickoloff, J. A. : XRCC3 controls the fidelity of homologous recombination: roles for XRCC3 in late stages of recombination.

[0291] Further studies establishing the function and utilities of XRCC3 are found in John Hopkins OMIM database record ID 600675, and in cited publications numbered 501–502, 503–504 and 505–506 listed in the bibliography section

hereinbelow, which are also hereby incorporated by reference. Rho GTPase Activating Protein 5 (ARHGAP5, Accession XM_085082) is another VGAM18 host target gene. ARHGAP5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ARHGAP5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARHGAP5 BINDING SITE, designated SEQ ID:321, to the nucleotide sequence of VGAM18 RNA, herein designated VGAM RNA, also designated SEQ ID:19.

[0292] Another function of VGAM18 is therefore inhibition of Rho GTPase Activating Protein 5 (ARHGAP5, Accession XM_085082). Accordingly, utilities of VGAM18 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARHGAP5. EFA6R (Accession NM_015310) is another VGAM18 host target gene. EFA6R BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EFA6R, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EFA6R BINDING SITE, designated SEQ ID:140, to the nu-

cleotide sequence of VGAM18 RNA, herein designated VGAM RNA, also designated SEQ ID:19.

[0293] Another function of VGAM18 is therefore inhibition of EFA6R (Accession NM_015310). Accordingly, utilities of VGAM18 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EFA6R. KIAA0903 (Accession XM_049251) is another VGAM18 host target gene. KIAA0903 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0903, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0903 BINDING SITE, designated SEQ ID:294, to the nucleotide sequence of VGAM18 RNA, herein designated VGAM RNA, also designated SEQ ID:19.

[0294] Another function of VGAM18 is therefore inhibition of KIAA0903 (Accession XM_049251). Accordingly, utilities of VGAM18 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0903. KIAA1244 (Accession XM_050424) is another VGAM18 host target gene. KIAA1244 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by KIAA1244, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1244 BINDING SITE, designated SEQ ID:295, to the nucleotide sequence of VGAM18 RNA, herein designated VGAM RNA, also designated SEQ ID:19.

[0295] Another function of VGAM18 is therefore inhibition of KIAA1244 (Accession XM_050424). Accordingly, utilities of VGAM18 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1244. Rpo1-2 (Accession NM_032212) is another VGAM18 host target gene. Rpo1-2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by Rpo1-2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of Rpo1-2 BINDING SITE, designated SEQ ID:214, to the nucleotide sequence of VGAM18 RNA, herein designated VGAM RNA, also designated SEQ ID:19.

[0296] Another function of VGAM18 is therefore inhibition of Rpo1-2 (Accession NM_032212). Accordingly, utilities of

VGAM18 include diagnosis, prevention and treatment of diseases and clinical conditions associated with Rpo1-2. LOC115574 (Accession XM_056240) is another VGAM18 host target gene. LOC115574 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC115574, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC115574 BINDING SITE, designated SEQ ID:303, to the nucleotide sequence of VGAM18 RNA, herein designated VGAM RNA, also designated SEQ ID:19.

[0297] Another function of VGAM18 is therefore inhibition of LOC115574 (Accession XM_056240). Accordingly, utilities of VGAM18 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC115574. LOC144144 (Accession XM_012034) is another VGAM18 host target gene. LOC144144 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC144144, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC144144 BINDING SITE, designated SEQ ID:260, to the nucleotide sequence of VGAM18 RNA, herein designated VGAM RNA, also designated SEQ ID:19.

[0298] Another function of VGAM18 is therefore inhibition of LOC144144 (Accession XM_012034). Accordingly, utilities of VGAM18 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144144. LOC148254 (Accession XM_086121) is another VGAM18 host target gene. LOC148254 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC148254, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148254 BINDING SITE, designated SEQ ID:329, to the nucleotide sequence of VGAM18 RNA, herein designated VGAM RNA, also designated SEQ ID:19.

[0299] Another function of VGAM18 is therefore inhibition of LOC148254 (Accession XM_086121). Accordingly, utilities of VGAM18 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148254. LOC157624 (Accession XM_098801) is another VGAM18 host target gene. LOC157624 BINDING

SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC157624, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157624 BINDING SITE, designated SEQ ID:359, to the nucleotide sequence of VGAM18 RNA, herein designated VGAM RNA, also designated SEQ ID:19.

[0300] Another function of VGAM18 is therefore inhibition of LOC157624 (Accession XM_098801). Accordingly, utilities of VGAM18 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157624. LOC220486 (Accession XM_165391) is another VGAM18 host target gene. LOC220486 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC220486, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220486 BINDING SITE, designated SEQ ID:374, to the nucleotide sequence of VGAM18 RNA, herein designated VGAM RNA, also designated SEQ ID:19.

[0301] Another function of VGAM18 is therefore inhibition of

LOC220486 (Accession XM_165391). Accordingly, utilities of VGAM18 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220486. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 19 (VGAM19) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0302] VGAM19 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM19 was detected is described hereinabove with reference to Figs. 1–8.

[0303] VGAM19 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Immunodeficiency Virus 1. VGAM19 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0304] VGAM19 gene encodes a VGAM19 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM19 precursor RNA does not encode a protein. A nucleotide

sequence identical or highly similar to the nucleotide sequence of VGAM19 precursor RNA is designated SEQ ID:5, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:5 is located at position 2168 relative to the genome of Human Immunodeficiency Virus 1.

[0305] VGAM19 precursor RNA folds onto itself, forming VGAM19 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0306] An enzyme complex designated DICER COMPLEX, `dices` the VGAM19 folded precursor RNA into VGAM19 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 60%) nucleotide se-

quence of VGAM19 RNA is designated SEQ ID:20, and is provided hereinbelow with reference to the sequence listing part.

[0307] VGAM19 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM19 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM19 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[0308] VGAM19 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM19 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM19 RNA is an accurate or a partial inverted-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustra-

tion only, and is not meant to be limiting – VGAM19 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM19 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[0309] The complementary binding of VGAM19 RNA, herein designated VGAM RNA, to host target binding sites on VGAM19 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM19 host target RNA into VGAM19 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0310] It is appreciated that VGAM19 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM19 host target genes. The mRNA of each one of this plurality of VGAM19 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-

plementary to VGAM19 RNA, herein designated VGAM RNA, and which when bound by VGAM19 RNA causes inhibition of translation of respective one or more VGAM19 host target proteins.

- [0311] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM19 gene, herein designated VGAM GENE, on one or more VGAM19 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).
- [0312] It is yet further appreciated that a function of VGAM19 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,

utilities of VGAM19 include diagnosis, prevention and treatment of viral infection by Human Immunodeficiency Virus 1. Specific functions, and accordingly utilities, of VGAM19 correlate with, and may be deduced from, the identity of the host target genes which VGAM19 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0313] Nucleotide sequences of the VGAM19 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM19 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM19 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM19 are further described hereinbelow with reference to Table 1.

[0314] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM19 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM19 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0315] As mentioned hereinabove with reference to Fig. 1, a function of VGAM19 gene, herein designated VGAM is in-

hibition of expression of VGAM19 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM19 correlate with, and may be deduced from, the identity of the target genes which VGAM19 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[0316] Amylo-1, 6-glucosidase, 4-alpha-glucanotransferase (glycogen debranching enzyme, glycogen storage disease type III) (AGL, Accession NM_000028) is a VGAM19 host target gene. AGL BINDING SITE1 through AGL BINDING SITE6 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by AGL, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AGL BINDING SITE1 through AGL BINDING SITE6, designated SEQ ID:31, SEQ ID:43, SEQ ID:44, SEQ ID:45, SEQ ID:46 and SEQ ID:47 respectively, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0317] A function of VGAM19 is therefore inhibition of Amylo-1, 6-glucosidase, 4-alpha-glucanotransferase (glycogen debranching enzyme, glycogen storage disease type III) (AGL, Accession NM_000028). Accordingly, utilities of

VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AGL.

Cockayne Syndrome 1 (classical) (CKN1, Accession NM_000082) is another VGAM19 host target gene. CKN1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CKN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CKN1 BINDING SITE, designated SEQ ID:32, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0318] Another function of VGAM19 is therefore inhibition of Cockayne Syndrome 1 (classical) (CKN1, Accession NM_000082). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CKN1. Hedgehog Interacting Protein (HHIP, Accession NM_022475) is another VGAM19 host target gene. HHIP BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by HHIP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the

nucleotide sequences of HHIP BINDING SITE, designated SEQ ID:189, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0319] Another function of VGAM19 is therefore inhibition of Hedgehog Interacting Protein (HHIP, Accession NM_022475), a gene which is involved in many fundamental processes in embryonic development, including anteroposterior patterns of limbs and regulation of left-right asymmetry. Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HHIP. The function of HHIP has been established by previous studies. Chuang and McMahon (1999) cloned a mouse hedgehog-interacting protein cDNA from a limb bud cDNA expression library. They determined that the Hip cDNA encodes a type I transmembrane glycoprotein, which is expressed in all hedgehog target tissues and binds all 3 mammalian hedgehog proteins (SHH, 600725; IHH, 600726; DHH, 605423) with an affinity similar to that of the Ptc protein (OMIM Ref. No. 601309), which is also a component of the Hh signaling pathway. Like Ptc, Hip expression is upregulated in response to Hh signaling. Ectopic expression of Hip in transgenic mice results in severe skeletal defects

similar to those observed in Indian hedgehog (IHH) mutants, demonstrating that Hip is involved in the attenuation of hedgehog signaling. By database searching with the mouse Hip sequence as query, followed by RT-PCR and RACE analysis using human adult testis cDNA, Bak et al. (2001) cloned a HIP cDNA encoding a deduced 700-amino acid protein that shares 94% sequence identity with mouse Hip. By RT-PCR analysis, HIP expression was detected in all fetal and adult tissues examined except fetal ovary and at very low levels in placenta.

[0320] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0321] Bak, M.; Hansen, C.; Henriksen, K. F.; Tommerup, N. : The human hedgehog-interacting protein gene: structure and chromosome mapping to 4q31.21-q31.3. *Cytogenet. Cell Genet.* 92: 300-303, 2001. ; and

[0322] Chuang, P.-T.; McMahon, A. P. : Vertebrate hedgehog signalling modulated by induction of a hedgehog-binding protein. *Nature* 397: 617-621, 1999.

[0323] Further studies establishing the function and utilities of HHIP are found in John Hopkins OMIM database record ID 606178, and in cited publications numbered 193-194

listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Interferon, Alpha 1 (IFNA1, Accession NM_024013) is another VGAM19 host target gene. IFNA1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IFNA1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IFNA1 BINDING SITE, designated SEQ ID:194, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0324] Another function of VGAM19 is therefore inhibition of Interferon, Alpha 1 (IFNA1, Accession NM_024013), a gene which is produced by macrophages and has antiviral activities. Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IFNA1. The function of IFNA1 has been established by previous studies. Leukocyte interferon is produced predominantly by B lymphocytes. Immune interferon (IFN-gamma; 147570) is produced by mitogen- or antigen-stimulated T lymphocytes. Using radioactive probes from purified cDNA clones of interferons, Owerbach et al. (1981) located at least 8 leukocyte inter-

feron genes and a fibroblast interferon gene on chromosome 9. Shows et al. (1982) found that the alpha- and beta-interferon genes are on 9p. The mapping to 9pter-q12 was accomplished by blot hybridization of cloned interferon cDNA to DNA from human-mouse cell hybrids with a translocation involving chromosome 9. There are about 10 linked genes for IFA. Lawn et al. (1981) sequenced 2 closely linked genes for leukocyte interferon. They were about 12 kb apart and each had no intervening sequences. Two other IFAs are known to be about 5 kb apart. Homology exists among the interferon genes. By in situ hybridization, Trent et al. (1982) localized IFL and IFF (OMIM Ref. No. 147640) to 9p21-pter and IFI to 12q24.1. From studies of patients with acute monocytic leukemia and t(9;11)(p22;q23), Diaz et al. (1986) concluded that alpha-interferon is in region 9p21-p13. Ohlsson et al. (1985) put the number of IFL genes at 15 to 30 but indicated that to some extent the large number of different sequences that have been identified may be on the basis of polymorphism. They demonstrated a number of DNA polymorphisms (RFLPs) and used them to show close proximity of the IFL and IFF loci. To define better the rearrangements and deletions in the region of the interferon

genes on 9p in malignancies, Fountain et al. (1992) did linkage, pulsed field gel electrophoresis, and fluorescence in situ hybridization of markers in that vicinity. Olopade et al. (1992) referred to the location of the cluster of interferon genes as 9p22. The interferon cluster comprises about 26 interferon- α , - ω (IFNW; 147553), and - β -1 (IFNB1; 147640) genes, as well as the gene for methylthioadenosine phosphorylase (MTAP; 156540). The IFNB1 gene is present in single copy, whereas the IFNA and IFNW genes are present in multiple functional copies as well as pseudogenes, which are interspersed. Olopade et al. (1992) found by deletion mapping that the IFNA1 gene is at the extreme centromeric end of the cluster, whereas IFNB1 is at the extreme telomeric end. From a YAC clone contig located on 9p, Diaz et al. (1994) mapped 26 interferon genes and pseudogenes, accounting for all except 1 of the IFN sequences previously reported by other authors, plus an additional IFN- ω pseudogene. The most distal gene on 9p is IFNB and the most proximal one is the pseudogene IFNWP19. The direction of transcription for the 20 most distal IFN sequences is toward the telomere and for the 6 most proximal sequences, toward the centromere. Several regions of the cluster show

evidence of ancestral duplication events. The successful use of intranasal alpha-2-interferon produced by recombinant DNA technology in the prophylaxis of the common cold was reported by Douglas et al. (1986) and Hayden et al. (1986). Siegal et al. (1999) demonstrated that purified interferon-producing cells were the CD4(+)CD11c(-) type 2 dendritic cell precursors, which produce 200 to 1,000 times more interferon than other blood cells after microbial challenge. Dendritic cell precursors are thus an effector cell type of the immune system, critical for antiviral and antitumor immune responses. Diaz and Bohlander (1993) tabulated the nomenclature of the human interferon genes. Thirteen functional genes and 1 pseudogene (IFNAP22) in the alpha-interferon family of type I interferon genes were listed. Diaz et al. (1994) and Diaz et al. (1996) provided an update of the nomenclature of the interferon genes and pseudogenes

[0325] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0326] Siegal, F. P.; Kadowaki, N.; Shodell, M.; Fitzgerald-Bocarsly, P. A.; Shah, K.; Ho, S.; Antonenko, S.; Liu, Y.-J. : The nature of the principal type 1 interferon-producing

cells in human blood. Science 284: 1835–1837, 1999. ;
and

[0327] Diaz, M. O.; Bohlander, S.; Allen, G. : Nomenclature of the human interferon genes. J. Interferon Cytokine Res. 16: 179–180, 1996.

[0328] Further studies establishing the function and utilities of IFNA1 are found in John Hopkins OMIM database record ID 147660, and in cited publications numbered 588, 589, 590–600, 79, 601–602, 560, 561, 605–607, 56 and 608–612 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Potassium Inwardly-rectifying Channel, Subfamily J, Member 6 (KCNJ6, Accession NM_002240) is another VGAM19 host target gene. KCNJ6 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KCNJ6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCNJ6 BINDING SITE, designated SEQ ID:60, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0329] Another function of VGAM19 is therefore inhibition of

Potassium Inwardly-rectifying Channel, Subfamily J, Member 6 (KCNJ6, Accession NM_002240), a gene which may be involved in the regulation of insulin secretion by glucose and/or neurotransmitters. Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNJ6. The function of KCNJ6 has been established by previous studies. ATP-sensitive potassium channels, also called K(ATP) channels, are closed by an increase in the intracellular ATP concentration of the cell and thereby provide a means of linking cellular metabolism to the electrical excitability of the plasma membrane. Sakura et al. (1995) stated that their physiologic function is best understood in the pancreatic beta-cell where they play a key role in the regulation of insulin secretion in response to nutrients. Closure of K(ATP) channels, as the result of metabolically generated ATP, produces membrane depolarization. This leads to activation of voltage-sensitive Ca^{2+} channels, Ca^{2+} influx, and ultimately insulin release. Sakura et al. (1995) cloned the KCNJ6 gene, which encodes a putative subunit of a human ATP-sensitive K-channel expressed in brain and beta cells, and characterized its exon/intron structure. By screening of a somatic

cell mapping panel and fluorescence in situ hybridization, they placed the gene on 21q22.1–q22.2. Analysis of SS-CPs revealed the presence of 2 silent polymorphisms (pro149: CCG–CCA and asp328: GAC–GAT) with similar frequencies in normal and noninsulin-dependent diabetic patients. The weaver mutation, discovered by Lane (1964), had been studied intensively for more than 25 years (Rakic and Sidman, 1973) for insights into the normal processes of neural development and differentiation. Homozygous animals suffer from severe ataxia that is obvious by about the second postnatal week. The cerebellum of these animals is drastically reduced in size due to depletion of the major cell type of cerebellum, the granule cell neuron. Heterozygous animals are not ataxic but have an intermediate number of surviving granule cells. Patil et al. (1995), and other workers before them, found that the overall expression pattern of the Girk2 gene corresponds closely to the pattern of phenotypic effects in weaver mice. Expression in the cerebellum, substantia nigra, and testes is associated with a developmental loss of cells in those tissues. Expression of Girk2 in the cortex is consistent with seizures that affect weaver mice. Goldowitz and Smeyne (1995) diagrammed the developmental events in

the early postnatal cerebellum in wildtype and weaver mice, the expression pattern of Girk2 mRNA in adult brain, and the proposed role of Girk2 in normal and abnormal granule cell differentiation.

[0330] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0331] Bandmann, O.; Davis, M. B.; Marsden, C. D.; Wood, N. W. : The human homologue of the Weaver mouse gene in familial and sporadic Parkinson's disease. *Neuroscience* 72: 877–879, 1996. ; and

[0332] Goldowitz, D.; Smeyne, R. J. : Tune into the weaver channel. *Nature Genet.* 11: 107–109, 1995.

[0333] Further studies establishing the function and utilities of KCNJ6 are found in John Hopkins OMIM database record ID 600877, and in cited publications numbered 131, 302–30 and 506–309 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Orthopedia Homolog (*Drosophila*) (OTP, Accession NM_032109) is another VGAM19 host target gene. OTP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by OTP, corresponding to a HOST TARGET binding site such as BINDING

SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OTP BINDING SITE, designated SEQ ID:212, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0334] Another function of VGAM19 is therefore inhibition of Orthopedia Homolog (Drosophila) (OTP, Accession NM_032109), a gene which involves in the development of the forebrain and spinal cord. Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OTP. The function of OTP has been established by previous studies. Homeodomain genes are helix–turn–helix transcription factors that play key roles in the specification of cell fates. In the central nervous system, homeodomain genes not only position cells along an axis, but also specify cell migration patterns and may influence axonal connectivity. In an effort to identify novel homeodomain genes involved in the development of the human central nervous system, Lin et al. (1999) cloned, characterized, and mapped the human homolog of the murine homeodomain gene Orthopedia (Otp), whose product is found in multiple cell groups within the mouse hypothalamus, amygdala, and

brain stem. The human OTP cDNA encodes a protein of 325 amino acids. The deduced amino acid sequence is 99% homologous to mouse Otp and demonstrated a high degree of conservation when compared to sea urchin and *Drosophila* Otp proteins. A single putative OTP gene product was found in 17-week human fetal brain tissue by Western blot analysis using a novel polyclonal antibody raised against a conserved 13-amino acid sequence in the C terminus of the OTP protein. Expression in the developing human hypothalamus was confirmed by immunohistochemistry. Lin et al. (1999) mapped the human OTP gene to chromosome 5q13.3 using analysis of a radiation hybrid panel and by fluorescence in situ hybridization. Animal model experiments lend further support to the function of OTP. Acampora et al. (1999) generated mice deficient in Otp by homologous recombination. Homozygous Otp $-/-$ mice died soon after birth and displayed progressive impairment of crucial neuroendocrine developmental events such as reduced cell proliferation, abnormal cell migration, and failure in terminal differentiation of the parvocellular and magnocellular neurons of the anterior periventricular, paraventricular, supraoptic, and arcuate nuclei. Acampora et al. (1999) suggested that Otp and

Sim1 (OMIM Ref. No. 603128) are required to maintain Brn2 (OMIM Ref. No. 600494) expression which, in turn, is required for neuronal cell lineages secreting oxytocin (OMIM Ref. No. 167050), arginine vasopressin (OMIM Ref. No. 192340), and corticotropin-releasing (OMIM Ref. No. 122560) hormones.

[0335] It is appreciated that the abovementioned animal model for OTP is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[0336] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0337] Acampora, D.; Postiglione, M. P.; Avantaggiato, V.; Di Bonito, M.; Vaccarino, F. M.; Michaud, J.; Simeone, A. : Progressive impairment of developing neuroendocrine cell lineages in the hypothalamus of mice lacking the Orthopedia gene. Genes Dev. 13: 2787–2800, 1999. ; and

[0338] Lin, X.; State, M. W.; Vaccarino, F. M.; Greally, J.; Hass, M.; Leckman, J. F. : Identification, chromosomal assignment, and expression analysis of the human homeodomain-containing gene.

[0339] Further studies establishing the function and utilities of

OTP are found in John Hopkins OMIM database record ID 604529, and in cited publications numbered 313–314 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Ras Homolog Enriched In Brain 2 (RHEB2, Accession NM_005614) is another VGAM19 host target gene. RHEB2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by RHEB2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RHEB2 BINDING SITE, designated SEQ ID:94, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0340] Another function of VGAM19 is therefore inhibition of Ras Homolog Enriched In Brain 2 (RHEB2, Accession NM_005614). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RHEB2. Ankyrin Repeat Domain 6 (ANKRD6, Accession NM_014942) is another VGAM19 host target gene. ANKRD6 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ANKRD6, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ANKRD6 BINDING SITE, designated SEQ ID:137, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0341] Another function of VGAM19 is therefore inhibition of Ankyrin Repeat Domain 6 (ANKRD6, Accession NM_014942). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ANKRD6. Ecotropic Viral Integration Site 5 (EVI5, Accession NM_005665) is another VGAM19 host target gene. EVI5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EVI5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EVI5 BINDING SITE, designated SEQ ID:95, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0342] Another function of VGAM19 is therefore inhibition of Ecotropic Viral Integration Site 5 (EVI5, Accession

NM_005665). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EVI5. FLJ00026 (Accession XM_036307) is another VGAM19 host target gene.

FLJ00026 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ00026, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ00026 BINDING SITE, designated SEQ ID:270, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0343] Another function of VGAM19 is therefore inhibition of FLJ00026 (Accession XM_036307). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ00026. Glycoprotein V (platelet) (GP5, Accession NM_004488) is another VGAM19 host target gene. GP5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GP5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GP5 BINDING

SITE, designated SEQ ID:84, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0344] Another function of VGAM19 is therefore inhibition of Glycoprotein V (platelet) (GP5, Accession NM_004488). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GP5. KH Domain Containing, RNA Binding, Signal Transduction Associated 3 (KHDRBS3, Accession NM_006558) is another VGAM19 host target gene. KHDRBS3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KHDRBS3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KHDRBS3 BINDING SITE, designated SEQ ID:107, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0345] Another function of VGAM19 is therefore inhibition of KH Domain Containing, RNA Binding, Signal Transduction Associated 3 (KHDRBS3, Accession NM_006558). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associ-

ated with KHDRBS3. KIAA0254 (Accession NM_014758) is another VGAM19 host target gene. KIAA0254 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0254, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0254 BINDING SITE, designated SEQ ID:132, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0346] Another function of VGAM19 is therefore inhibition of KIAA0254 (Accession NM_014758). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0254. KIAA1165 (Accession XM_041162) is another VGAM19 host target gene. KIAA1165 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1165, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1165 BINDING SITE, designated SEQ ID:281, to the nucleotide sequence of VGAM19 RNA, herein designated

VGAM RNA, also designated SEQ ID:20.

[0347] Another function of VGAM19 is therefore inhibition of KIAA1165 (Accession XM_041162). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1165. KIAA1240 (Accession XM_039676) is another VGAM19 host target gene. KIAA1240 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1240, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1240 BINDING SITE, designated SEQ ID:277, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0348] Another function of VGAM19 is therefore inhibition of KIAA1240 (Accession XM_039676). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1240. NYD-SP15 (Accession NM_030911) is another VGAM19 host target gene. NYD-SP15 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NYD-SP15, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NYD-SP15 BINDING SITE, designated SEQ ID:209, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0349] Another function of VGAM19 is therefore inhibition of NYD-SP15 (Accession NM_030911). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NYD-SP15. Pellino Homolog 1 (Drosophila) (PELI1, Accession NM_020651) is another VGAM19 host target gene. PELI1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PELI1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PELI1 BINDING SITE, designated SEQ ID:175, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0350] Another function of VGAM19 is therefore inhibition of Pellino Homolog 1 (Drosophila) (PELI1, Accession NM_020651). Accordingly, utilities of VGAM19 include di-

agnosis, prevention and treatment of diseases and clinical conditions associated with PELI1. PRO0159 (Accession NM_014118) is another VGAM19 host target gene.

PRO0159 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by PRO0159, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO0159 BINDING SITE, designated SEQ ID:125, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0351] Another function of VGAM19 is therefore inhibition of PRO0159 (Accession NM_014118). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO0159. Rac GTPase Activating Protein 1 (RACGAP1, Accession NM_013277) is another VGAM19 host target gene. RAC-GAP1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by RAC-GAP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RACGAP1 BINDING SITE, designated SEQ

ID:121, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0352] Another function of VGAM19 is therefore inhibition of Rac GTPase Activating Protein 1 (RACGAP1, Accession NM_013277). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RACGAP1. Stromal Cell Derived Factor Receptor 1 (SDFR1, Accession NM_012428) is another VGAM19 host target gene. SDFR1 BINDING SITE1 and SDFR1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by SDFR1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SDFR1 BINDING SITE1 and SDFR1 BINDING SITE2, designated SEQ ID:118 and SEQ ID:151 respectively, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0353] Another function of VGAM19 is therefore inhibition of Stromal Cell Derived Factor Receptor 1 (SDFR1, Accession NM_012428). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SDFR1. SV2B (Accession

NM_014848) is another VGAM19 host target gene. SV2B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SV2B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SV2B BINDING SITE, designated SEQ ID:136, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0354] Another function of VGAM19 is therefore inhibition of SV2B (Accession NM_014848). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SV2B. LOC130589 (Accession NM_138801) is another VGAM19 host target gene. LOC130589 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC130589, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC130589 BINDING SITE, designated SEQ ID:244, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0355] Another function of VGAM19 is therefore inhibition of LOC130589 (Accession NM_138801). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC130589. LOC200107 (Accession XM_114121) is another VGAM19 host target gene. LOC200107 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200107, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200107 BINDING SITE, designated SEQ ID:364, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0356] Another function of VGAM19 is therefore inhibition of LOC200107 (Accession XM_114121). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200107. LOC203340 (Accession XM_114688) is another VGAM19 host target gene. LOC203340 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC203340, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203340 BINDING SITE, designated SEQ ID:368, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0357] Another function of VGAM19 is therefore inhibition of LOC203340 (Accession XM_114688). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC203340. LOC221271 (Accession XM_166307) is another VGAM19 host target gene. LOC221271 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221271, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221271 BINDING SITE, designated SEQ ID:380, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0358] Another function of VGAM19 is therefore inhibition of LOC221271 (Accession XM_166307). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC221271. LOC254778 (Accession XM_171193) is another VGAM19 host target gene. LOC254778 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254778, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254778 BINDING SITE, designated SEQ ID:400, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0359] Another function of VGAM19 is therefore inhibition of LOC254778 (Accession XM_171193). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254778. LOC51312 (Accession NM_018579) is another VGAM19 host target gene. LOC51312 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC51312, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51312 BINDING SITE, designated SEQ ID:164, to the nucleotide sequence of VGAM19 RNA, herein designated

VGAM RNA, also designated SEQ ID:20.

[0360] Another function of VGAM19 is therefore inhibition of LOC51312 (Accession NM_018579). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51312. LOC91286 (Accession XM_037444) is another VGAM19 host target gene. LOC91286 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91286, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91286 BINDING SITE, designated SEQ ID:273, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0361] Another function of VGAM19 is therefore inhibition of LOC91286 (Accession XM_037444). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91286. LOC92223 (Accession XM_043674) is another VGAM19 host target gene. LOC92223 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92223, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92223 BINDING SITE, designated SEQ ID:286, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0362] Another function of VGAM19 is therefore inhibition of LOC92223 (Accession XM_043674). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92223. LOC92482 (Accession XM_045310) is another VGAM19 host target gene. LOC92482 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC92482, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92482 BINDING SITE, designated SEQ ID:288, to the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, also designated SEQ ID:20.

[0363] Another function of VGAM19 is therefore inhibition of LOC92482 (Accession XM_045310). Accordingly, utilities of VGAM19 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC92482. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 20 (VGAM20) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0364] VGAM20 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM20 was detected is described hereinabove with reference to Figs. 1–8.

[0365] VGAM20 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Immunodeficiency Virus 1. VGAM20 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0366] VGAM20 gene encodes a VGAM20 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM20 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM20 precursor RNA is designated SEQ ID:6,

and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:6 is located at position 587 relative to the genome of Human Immunodeficiency Virus 1.

[0367] VGAM20 precursor RNA folds onto itself, forming VGAM20 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0368] An enzyme complex designated DICER COMPLEX, `dices` the VGAM20 folded precursor RNA into VGAM20 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 84%) nucleotide sequence of VGAM20 RNA is designated SEQ ID:21, and is provided hereinbelow with reference to the sequence list-

ing part.

[0369] VGAM20 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM20 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM20 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[0370] VGAM20 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM20 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM20 RNA is an accurate or a partial inverted-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM20 RNA, herein designated VGAM RNA, may have a different num-

ber of host target binding sites in untranslated regions of a VGAM20 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[0371] The complementary binding of VGAM20 RNA, herein designated VGAM RNA, to host target binding sites on VGAM20 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM20 host target RNA into VGAM20 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0372] It is appreciated that VGAM20 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM20 host target genes. The mRNA of each one of this plurality of VGAM20 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM20 RNA, herein designated VGAM RNA, and which when bound by VGAM20 RNA causes in–

hibition of translation of respective one or more VGAM20 host target proteins.

[0373] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM20 gene, herein designated VGAM GENE, on one or more VGAM20 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[0374] It is yet further appreciated that a function of VGAM20 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM20 include diagnosis, prevention and treatment of viral infection by Human Immunodeficiency

Virus 1. Specific functions, and accordingly utilities, of VGAM20 correlate with, and may be deduced from, the identity of the host target genes which VGAM20 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0375] Nucleotide sequences of the VGAM20 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM20 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM20 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM20 are further described hereinbelow with reference to Table 1.

[0376] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM20 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM20 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0377] As mentioned hereinabove with reference to Fig. 1, a function of VGAM20 gene, herein designated VGAM is inhibition of expression of VGAM20 target genes. It is appreciated that specific functions, and accordingly utilities,

of VGAM20 correlate with, and may be deduced from, the identity of the target genes which VGAM20 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[0378] Attractin (ATRN, Accession NM_139321) is a VGAM20 host target gene. ATRN BINDING SITE1 and ATRN BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ATRN, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATRN BINDING SITE1 and ATRN BINDING SITE2, designated SEQ ID:248 and SEQ ID:248 respectively, to the nucleotide sequence of VGAM20 RNA, herein designated VGAM RNA, also designated SEQ ID:21.

[0379] A function of VGAM20 is therefore inhibition of Attractin (ATRN, Accession NM_139321), a gene which is involved in the initial immune cell clustering during inflammatory response. Accordingly, utilities of VGAM20 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATRN. The function of ATRN has been established by previous studies. Attractin is a human serum glycoprotein that is rapidly expressed on

activated T cells and released extracellularly after 48 to 72 hours. Duke-Cohan et al. (1998) cloned attractin and found that, as in its natural serum form, it mediates the spreading of monocytes that becomes the focus for the clustering of nonproliferating T lymphocytes. There are 2 mRNA species with hematopoietic tissue-specific expression that code for a 134-kD protein with a putative serine protease catalytic serine, 4 EGF-like motifs, a CUB domain, a C-type lectin domain, and a domain homologous with the ligand-binding region of the common gamma cytokine chain. Except for the last 2 domains, the overall structure shares high homology with a protein of *Caenorhabditis elegans*, suggesting that attractin has evolved new domains and functions in parallel with the development of cell-mediated immunity. When attractin was identified as the product of the murine 'mahogany' gene with connections to control of pigmentation and energy metabolism, and the 'mahogany' product was identified and shown to be a transmembrane protein, the possibility of a human membrane attractin in addition to the secreted form was raised. Tang et al. (2000) described the complete genomic sequence of attractin, focusing in particular on the exons coding for the 3-prime region, and

showed how both human membrane and secreted attractin arise as a result of alternate splicing of the same gene. They found that soluble attractin arises from transcription of 25 sequential exons on 20p13, where the 3-prime terminal exon contains sequence from a long interspersed nuclear element-1 (OMIM Ref. No. LINE-1) retrotransposon insertion that includes a stop codon and a polyadenylation signal. The mRNA isoform for membrane attraction splices over the LINE-1 exon and includes 5 exons encoding transmembrane and cytoplasmic domains with organization and coding potential almost identical to that of the mouse gene. The relative abundance of soluble and transmembrane isoforms measured by RT-PCR is differentially regulated in lymphoid tissues. Because activation of peripheral blood leukocytes with phytohemagglutinin induces strong expression of cell surface attractin followed by release of soluble attractin, these results suggested to Tang et al. (2000) that LINE-1 insertion, a genomic event unique to mammals, provided an evolutionarily mechanism for regulating cell interactions during an inflammatory reaction.

[0380] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [0381] Duke-Cohan, J. S.; Gu, J.; McLaughlin, D. F.; Xu, Y.; Freeman, G. J.; Schlossman, S. F. : Attractin (DPPT-L), a member of the CUB family of cell adhesion and guidance proteins, is secreted by activated human T lymphocytes and modulates immune cell interactions. *Proc. Nat. Acad. Sci.* 95: 11336–11341, 1998. ; and
- [0382] Tang, W.; Gunn, T. M.; McLaughlin, D. F.; Barsh, G. S.; Schlossman, S. F.; Duke-Cohan, J. S. : Secreted and membrane attractin result from alternative splicing of the human ATRN gene. *Pr.*
- [0383] Further studies establishing the function and utilities of ATRN are found in John Hopkins OMIM database record ID 603130, and in cited publications numbered 13–1 and 234 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. DKFZP564O0463 (Accession NM_014156) is another VGAM20 host target gene. DKFZP564O0463 BINDING SITE1 and DKFZP564O0463 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by DKFZP564O0463, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the comple–

mentarity of the nucleotide sequences of DKFZP564O0463 BINDING SITE1 and DKFZP564O0463 BINDING SITE2, designated SEQ ID:127 and SEQ ID:202 respectively, to the nucleotide sequence of VGAM20 RNA, herein designated VGAM RNA, also designated SEQ ID:21.

- [0384] Another function of VGAM20 is therefore inhibition of DKFZP564O0463 (Accession NM_014156). Accordingly, utilities of VGAM20 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP564O0463. HSPC014 (Accession NM_015932) is another VGAM20 host target gene. HSPC014 BINDING SITE1 and HSPC014 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by HSPC014, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSPC014 BINDING SITE1 and HSPC014 BINDING SITE2, designated SEQ ID:144 and SEQ ID:144 respectively, to the nucleotide sequence of VGAM20 RNA, herein designated VGAM RNA, also designated SEQ ID:21.
- [0385] Another function of VGAM20 is therefore inhibition of HSPC014 (Accession NM_015932). Accordingly, utilities of VGAM20 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with HSPC014. KIAA0040 (Accession NM_014656) is another VGAM20 host target gene. KIAA0040 BINDING SITE1 and KIAA0040 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by KIAA0040, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0040 BINDING SITE1 and KIAA0040 BINDING SITE2, designated SEQ ID:129 and SEQ ID:134 respectively, to the nucleotide sequence of VGAM20 RNA, herein designated VGAM RNA, also designated SEQ ID:21.

[0386] Another function of VGAM20 is therefore inhibition of KIAA0040 (Accession NM_014656). Accordingly, utilities of VGAM20 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0040. KIAA1908 (Accession XM_055834) is another VGAM20 host target gene. KIAA1908 BINDING SITE1 and KIAA1908 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by KIAA1908, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of KIAA1908 BINDING SITE1 and KIAA1908 BINDING SITE2, designated SEQ ID:302 and SEQ ID:302 respectively, to the nucleotide sequence of VGAM20 RNA, herein designated VGAM RNA, also designated SEQ ID:21.

[0387] Another function of VGAM20 is therefore inhibition of KIAA1908 (Accession XM_055834). Accordingly, utilities of VGAM20 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1908. MGC22014 (Accession XM_035307) is another VGAM20 host target gene. MGC22014 BINDING SITE1 and MGC22014 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by MGC22014, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC22014 BINDING SITE1 and MGC22014 BINDING SITE2, designated SEQ ID:269 and SEQ ID:293 respectively, to the nucleotide sequence of VGAM20 RNA, herein designated VGAM RNA, also designated SEQ ID:21.

[0388] Another function of VGAM20 is therefore inhibition of MGC22014 (Accession XM_035307). Accordingly, utilities of VGAM20 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

MGC22014. LOC116123 (Accession NM_138784) is another VGAM20 host target gene. LOC116123 BINDING SITE1 and LOC116123 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by LOC116123, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC116123 BINDING SITE1 and LOC116123 BINDING SITE2, designated SEQ ID:243 and SEQ ID:243 respectively, to the nucleotide sequence of VGAM20 RNA, herein designated VGAM RNA, also designated SEQ ID:21.

[0389] Another function of VGAM20 is therefore inhibition of LOC116123 (Accession NM_138784). Accordingly, utilities of VGAM20 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC116123. LOC149721 (Accession XM_086649) is another VGAM20 host target gene. LOC149721 BINDING SITE1 and LOC149721 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by LOC149721, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of LOC149721 BINDING SITE1 and LOC149721 BINDING SITE2, designated SEQ ID:334 and SEQ ID:354 respectively, to the nucleotide sequence of VGAM20 RNA, herein designated VGAM RNA, also designated SEQ ID:21.

[0390] Another function of VGAM20 is therefore inhibition of LOC149721 (Accession XM_086649). Accordingly, utilities of VGAM20 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149721. LOC220766 (Accession XM_165471) is another VGAM20 host target gene. LOC220766 BINDING SITE1 and LOC220766 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by LOC220766, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220766 BINDING SITE1 and LOC220766 BINDING SITE2, designated SEQ ID:375 and SEQ ID:375 respectively, to the nucleotide sequence of VGAM20 RNA, herein designated VGAM RNA, also designated SEQ ID:21.

[0391] Another function of VGAM20 is therefore inhibition of LOC220766 (Accession XM_165471). Accordingly, utilities

of VGAM20 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220766. LOC253351 (Accession XM_172774) is another VGAM20 host target gene. LOC253351 BINDING SITE1 and LOC253351 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by LOC253351, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253351 BINDING SITE1 and LOC253351 BINDING SITE2, designated SEQ ID:402 and SEQ ID:366 respectively, to the nucleotide sequence of VGAM20 RNA, herein designated VGAM RNA, also designated SEQ ID:21.

[0392] Another function of VGAM20 is therefore inhibition of LOC253351 (Accession XM_172774). Accordingly, utilities of VGAM20 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253351. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 21 (VGAM21) viral gene, which modulates expression of respective host target genes thereof,

the function and utility of which host target genes is known in the art.

[0393] VGAM21 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM21 was detected is described hereinabove with reference to Figs. 1–8.

[0394] VGAM21 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Immunodeficiency Virus 1. VGAM21 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0395] VGAM21 gene encodes a VGAM21 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM21 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM21 precursor RNA is designated SEQ ID:7, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:7 is located at position 7857 relative to the genome of Human Immunodeficiency Virus 1.

[0396] VGAM21 precursor RNA folds onto itself, forming VGAM21 folded precursor RNA, herein designated VGAM FOLDED

PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0397] An enzyme complex designated DICER COMPLEX, `dices` the VGAM21 folded precursor RNA into VGAM21 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 77%) nucleotide sequence of VGAM21 RNA is designated SEQ ID:22, and is provided hereinbelow with reference to the sequence listing part.

[0398] VGAM21 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM21 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM21 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a

5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[0399] VGAM21 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM21 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM21 RNA is an accurate or a partial inverted-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM21 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM21 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR

region, or in both 3`UTR and 5`UTR regions.

[0400] The complementary binding of VGAM21 RNA, herein designated VGAM RNA, to host target binding sites on VGAM21 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM21 host target RNA into VGAM21 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0401] It is appreciated that VGAM21 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM21 host target genes. The mRNA of each one of this plurality of VGAM21 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM21 RNA, herein designated VGAM RNA, and which when bound by VGAM21 RNA causes inhibition of translation of respective one or more VGAM21 host target proteins.

[0402] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM21 gene, herein designated VGAM GENE, on one or

more VGAM21 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[0403] It is yet further appreciated that a function of VGAM21 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM21 include diagnosis, prevention and treatment of viral infection by Human Immunodeficiency Virus 1. Specific functions, and accordingly utilities, of VGAM21 correlate with, and may be deduced from, the identity of the host target genes which VGAM21 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0404] Nucleotide sequences of the VGAM21 precursor RNA,

herein designated VGAM PRECURSOR RNA, and of the
`diced` VGAM21 RNA, herein designated VGAM RNA, and
a schematic representation of the secondary folding of
VGAM21 folded precursor RNA, herein designated VGAM
FOLDED PRECURSOR RNA, of VGAM21 are further de-
scribed hereinbelow with reference to Table 1.

[0405] Nucleotide sequences of host target binding sites, such as
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of
Fig. 1, found on VGAM21 host target RNA, and schematic
representation of the complementarity of each of these
host target binding sites to VGAM21 RNA, herein desig-
nated VGAM RNA, are described hereinbelow with refer-
ence to Table 2.

[0406] As mentioned hereinabove with reference to Fig. 1, a
function of VGAM21 gene, herein designated VGAM is in-
hibition of expression of VGAM21 target genes. It is ap-
preciated that specific functions, and accordingly utilities,
of VGAM21 correlate with, and may be deduced from, the
identity of the target genes which VGAM21 binds and in-
hibits, and the function of these target genes, as elabo-
rated hereinbelow.

[0407] KIAA1843 (Accession XM_030838) is a VGAM21 host tar-
get gene. KIAA1843 BINDING SITE is HOST TARGET bind-

ing site found in the 3' untranslated region of mRNA encoded by KIAA1843, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1843 BINDING SITE, designated SEQ ID:267, to the nucleotide sequence of VGAM21 RNA, herein designated VGAM RNA, also designated SEQ ID:22.

[0408] A function of VGAM21 is therefore inhibition of KIAA1843 (Accession XM_030838). Accordingly, utilities of VGAM21 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1843. Stromal Cell Derived Factor Receptor 1 (SDFR1, Accession NM_012428) is another VGAM21 host target gene. SDFR1 BINDING SITE1 and SDFR1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by SDFR1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SDFR1 BINDING SITE1 and SDFR1 BINDING SITE2, designated SEQ ID:117 and SEQ ID:150 respectively, to the nucleotide sequence of VGAM21 RNA, herein designated VGAM RNA, also designated SEQ ID:22.

[0409] Another function of VGAM21 is therefore inhibition of Stromal Cell Derived Factor Receptor 1 (SDFR1, Accession NM_012428). Accordingly, utilities of VGAM21 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SDFR1. LOC145622 (Accession XM_085186) is another VGAM21 host target gene.

LOC145622 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145622, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145622 BINDING SITE, designated SEQ ID:322, to the nucleotide sequence of VGAM21 RNA, herein designated VGAM RNA, also designated SEQ ID:22.

[0410] Another function of VGAM21 is therefore inhibition of LOC145622 (Accession XM_085186). Accordingly, utilities of VGAM21 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145622. LOC222681 (Accession XM_167116) is another VGAM21 host target gene. LOC222681 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC222681, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC222681 BINDING SITE, designated SEQ ID:386, to the nucleotide sequence of VGAM21 RNA, herein designated VGAM RNA, also designated SEQ ID:22.

[0411] Another function of VGAM21 is therefore inhibition of LOC222681 (Accession XM_167116). Accordingly, utilities of VGAM21 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC222681. LOC257507 (Accession XM_175204) is another VGAM21 host target gene. LOC257507 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC257507, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257507 BINDING SITE, designated SEQ ID:405, to the nucleotide sequence of VGAM21 RNA, herein designated VGAM RNA, also designated SEQ ID:22.

[0412] Another function of VGAM21 is therefore inhibition of LOC257507 (Accession XM_175204). Accordingly, utilities of VGAM21 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC257507. LOC257625 (Accession XM_175267) is another VGAM21 host target gene. LOC257625 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC257625, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257625 BINDING SITE, designated SEQ ID:406, to the nucleotide sequence of VGAM21 RNA, herein designated VGAM RNA, also designated SEQ ID:22.

[0413] Another function of VGAM21 is therefore inhibition of LOC257625 (Accession XM_175267). Accordingly, utilities of VGAM21 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257625. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 22 (VGAM22) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0414] VGAM22 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM22 was detected is described hereinabove with reference to Figs. 1–8.

[0415] VGAM22 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Immunodeficiency Virus 1. VGAM22 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0416] VGAM22 gene encodes a VGAM22 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM22 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM22 precursor RNA is designated SEQ ID:8, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:8 is located at position 8292 relative to the genome of Human Immunodeficiency Virus 1.

[0417] VGAM22 precursor RNA folds onto itself, forming VGAM22 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is

due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0418] An enzyme complex designated DICER COMPLEX, `dices` the VGAM22 folded precursor RNA into VGAM22 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 76%) nucleotide sequence of VGAM22 RNA is designated SEQ ID:23, and is provided hereinbelow with reference to the sequence listing part.

[0419] VGAM22 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM22 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM22 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[0420] VGAM22 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM22 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM22 RNA is an accurate or a partial inverted-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM22 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM22 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[0421] The complementary binding of VGAM22 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM22 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM22 host target RNA into VGAM22 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0422] It is appreciated that VGAM22 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM22 host target genes. The mRNA of each one of this plurality of VGAM22 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM22 RNA, herein designated VGAM RNA, and which when bound by VGAM22 RNA causes inhibition of translation of respective one or more VGAM22 host target proteins.

[0423] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM22 gene, herein designated VGAM GENE, on one or more VGAM22 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with

reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[0424] It is yet further appreciated that a function of VGAM22 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of viral infection by Human Immunodeficiency Virus 1. Specific functions, and accordingly utilities, of VGAM22 correlate with, and may be deduced from, the identity of the host target genes which VGAM22 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0425] Nucleotide sequences of the VGAM22 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM22 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of

VGAM22 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM22 are further described hereinbelow with reference to Table 1.

[0426] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM22 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM22 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0427] As mentioned hereinabove with reference to Fig. 1, a function of VGAM22 gene, herein designated VGAM is inhibition of expression of VGAM22 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM22 correlate with, and may be deduced from, the identity of the target genes which VGAM22 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[0428] Basic Transcription Element Binding Protein 1 (BTEB1, Accession NM_001206) is a VGAM22 host target gene. BTEB1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BTEB1, corresponding to a HOST TARGET binding site such as

BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BTEB1 BINDING SITE, designated SEQ ID:53, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0429] A function of VGAM22 is therefore inhibition of Basic Transcription Element Binding Protein 1 (BTEB1, Accession NM_001206). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BTEB1. Centrosomal Protein 2 (CEP2, Accession NM_007186) is another VGAM22 host target gene. CEP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CEP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CEP2 BINDING SITE, designated SEQ ID:112, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0430] Another function of VGAM22 is therefore inhibition of Centrosomal Protein 2 (CEP2, Accession NM_007186), a gene which interacts with TC10 and CDC42. Accordingly, utilities of VGAM22 include diagnosis, prevention and

treatment of diseases and clinical conditions associated with CEP2. The function of CEP2 has been established by previous studies. Using a yeast 2-hybrid screen on a mouse embryo cDNA library with TC10 (OMIM Ref. No. 605857) as the bait, followed by EST database searching, Joberty et al. (1999) identified cDNAs encoding human and mouse BORG1 (CEP2), BORG2 (CEP3; 606133), BORG3 (CEP5), BORG4 (CEP4; 605468), and BORG5 (CEP1). Sequence analysis predicted that the 210-amino acid BORG1 protein contains a CRIB motif followed by a conserved 12-residue BORG homology-1 (BH1) domain in its N terminus; an 11-amino acid BH2 domain in its central region; and a 22-residue BH3 domain in its C terminus. Northern blot analysis detected ubiquitous but variable expression of 1.8- and 2.0-kb BORG1 transcripts, with high levels in heart and low levels in pancreas and liver. By binding analysis, Joberty et al. (1999) confirmed that BORG1 interacts with TC10 and CDC42. Immunofluorescence microscopy demonstrated cytoplasmic expression of BORG1. BORG1 expression caused no dramatic changes in cell shape and a reduced abundance of stress fibers. Coexpression of BORG1 with CDC42 resulted in cells showing a 'porcupine' phenotype characterized by an

abundance of actin-filled spikes. By EST database searching with CEP1 as the probe, Hirsch et al. (2001) identified cDNAs encoding several CEPs, including CEP2. They referred to the BH2 and BH3 domains as CI and CII, respectively, and considered the BH1 domain to be part of an extended CRIB motif. Hirsch et al. (2001) proposed that these motifs are potential signaling domains. Fluorescence microscopy demonstrated cytoplasmic and membrane expression of CEP2 in keratinocytes, with notable localization in a perinuclear cytoplasmic compartment

[0431] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0432] Hirsch, D. S.; Pirone, D. M.; Burbelo, P. D. : A new family of Cdc42 effector proteins, CEPs, function in fibroblast and epithelial cell shape changes. *J. Biol. Chem.* 276: 875–883, 2001. ; and

[0433] Joberty, G.; Perlungher, R. R.; Macara, I. G. : The Borgs, a new family of Cdc42 and TC10 GTPase-interacting proteins. *Molec. Cell. Biol.* 19: 6585–6597, 1999.

[0434] Further studies establishing the function and utilities of CEP2 are found in John Hopkins OMIM database record ID 606132, and in cited publications numbered 289–29 and

279 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Extracellular Matrix Protein 1 (ECM1, Accession NM_004425) is another VGAM22 host target gene. ECM1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ECM1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ECM1 BINDING SITE, designated SEQ ID:82, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0435] Another function of VGAM22 is therefore inhibition of Extracellular Matrix Protein 1 (ECM1, Accession NM_004425). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ECM1. Endoglin (Osler-Rendu-Weber syndrome 1) (ENG, Accession NM_000118) is another VGAM22 host target gene. ENG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ENG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illus-

trates the complementarity of the nucleotide sequences of ENG BINDING SITE, designated SEQ ID:34, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0436] Another function of VGAM22 is therefore inhibition of Endoglin (Osler-Rendu-Weber syndrome 1) (ENG, Accession NM_000118). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ENG. Estrogen-related Receptor Gamma (ESRRG, Accession XM_039053) is another VGAM22 host target gene. ESRRG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ESRRG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ESRRG BINDING SITE, designated SEQ ID:276, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0437] Another function of VGAM22 is therefore inhibition of Estrogen-related Receptor Gamma (ESRRG, Accession XM_039053), a gene which Estrogen-related receptor gamma. Accordingly, utilities of VGAM22 include diagno-

sis, prevention and treatment of diseases and clinical conditions associated with ESRRG. The function of ESRRG has been established by previous studies. Members of the nuclear receptor superfamily are important regulators of development, cell proliferation, and physiology. During an analysis of the critical region of type IIa Usher syndrome (USH2A; 276901) at 1q41, Eudy et al. (1998) constructed a cDNA contig of ESRRG. Northern blot analysis detected a 5.5-kb ESRRG transcript in a variety of human adult and fetal tissues, with the highest level in fetal brain. The predicted 436-amino acid ESRRG protein, which is a member of the steroid/thyroid/retinoid receptor superfamily, is 76% identical to the orphan receptor ESRRB (OMIM Ref. No. 602167) and 63% identical to ESRRG (OMIM Ref. No. 601998). Heard et al. (2000) reported that the ESRRG mRNA is highly alternatively spliced at the 5-prime end, giving rise to a number of tissue-specific RNA species, some of which encode protein isoforms differing in the N-terminal region. Like ESRRG and ESRRB, ESRRG binds as a monomer to an ERR-alpha response element (ERRE). Hong et al. (1999) identified mouse *Esrrg*, which they called *Err3*, by yeast 2-hybrid screening using the transcriptional coactivator GRIP1 (OMIM Ref. No. 604597) as bait. The

putative full-length mouse Err3 contains 458 amino acids and is closely related to Err1 and Err2. All ERR family members share an almost identical DNA-binding domain, which shares 68% amino acid identity with that of estrogen receptor. Expression of Err3 in adult mouse was restricted; highest expression was observed in heart, kidney, and brain. In mouse embryo, no expression was observed at day 7, and highest expression occurred around days 11 to 15. Although Err3 is more closely related to Err2 than to Err1, the expression pattern for Err3 was similar to that of Err1 and distinct from that for Err2, suggesting a unique role for Err3 in development. Eudy et al. (1998) mapped the ESRRG gene to the USH2A critical region on chromosome 1q41.

[0438] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0439] Heard, D. J.; Norby, P. L.; Holloway, J.; Vissing, H. : Human ERR-gamma, a third member of the estrogen receptor-related receptor (ERR) subfamily of orphan nuclear receptors: tissue-specific isoforms are expressed during development in the adult. *Molec. Endocr.* 14: 382-392, 2000. ; and

- [0440] Eudy, J. D.; Yao, S.; Weston, M. D.; Ma-Edmonds, M.; Talmadge, C. B.; Cheng, J. J.; Kimberling, W. J.; Sumegi, J. : Isolation of a gene encoding a novel member of the nuclear receptor s.
- [0441] Further studies establishing the function and utilities of ESRRG are found in John Hopkins OMIM database record ID 602969, and in cited publications numbered 452-45 and 458-459 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Histone Deacetylase 4 (HDAC4, Accession NM_006037) is another VGAM22 host target gene. HDAC4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HDAC4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HDAC4 BINDING SITE, designated SEQ ID:98, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.
- [0442] Another function of VGAM22 is therefore inhibition of Histone Deacetylase 4 (HDAC4, Accession NM_006037), a gene which is responsible for the deacetylation of lysine residues on the n-terminal part of the core histones and

may mediate transcriptional regulation. Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HDAC4. The function of HDAC4 has been established by previous studies. Wang et al. (1999) cloned HDAC4 and demonstrated that its deacetylase activity requires histidine at residues 802 and 803. They determined that HDAC4 does not bind DNA directly, but rather through MEF2C (OMIM Ref. No. 600662) and MEF2D (OMIM Ref. No. 600663). Binding of the N terminus of HDAC4 to MEF2C represses MEF2C transcription activity. Fischle et al. (2002) showed that the catalytic domain of HDAC4 interacts with HDAC3 via the transcriptional corepressor NCOR2 (OMIM Ref. No. 600848). All experimental conditions leading to the suppression of HDAC4 binding to NCOR2 and to HDAC3 resulted in loss of enzymatic activity associated with HDAC4. These observations indicated that class II HDACs regulate transcription by bridging the enzymatically active NCOR2–HDAC3 complex and select transcription factors.

[0443] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

- [0444] Wang, A. H.; Bertos, N. R.; Vezmar, M.; Pelletier, N.; Crosato, M.; Heng, H. H.; Th'ng, J.; Han, J.; Yang, X.-J. : HDAC4, a human histone deacetylase related to yeast HDA1, is a transcriptional corepressor. *Molec. Cell. Biol.* 19: 7816–7827, 1999. ; and
- [0445] Fischle, W.; Dequiedt, F.; Hendzel, M. J.; Guenther, M. G.; Lazar, M. A.; Voelter, W.; Verdin, E. : Enzymatic activity associated with class II HDACs is dependent on a multiprotein comp.
- [0446] Further studies establishing the function and utilities of HDAC4 are found in John Hopkins OMIM database record ID 605314, and in cited publications numbered 50 and 521 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Interleukin 6 (interferon, beta 2) (IL6, Accession NM_000600) is another VGAM22 host target gene. IL6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IL6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IL6 BINDING SITE, designated SEQ ID:41, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ

ID:23.

[0447] Another function of VGAM22 is therefore inhibition of Interleukin 6 (interferon, beta 2) (IL6, Accession NM_000600), a gene which plays an essential role in the final differentiation of b-cells into ig-secreting cells. Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IL6. The function of IL6 has been established by previous studies. Whereas the 0.9-kb IFN-beta-1 mRNA is transcribed from an intron-free IFNB1 gene located on 9p (OMIM Ref. No. 147640), IFN-beta-2 is the translation product of a 1.3-kb mRNA derived from an intron-containing IFNB2 gene not located on chromosome 9. The IFN-beta-2 mRNA does not cross-hybridize with IFN-beta-1 cDNA probes and vice-versa. Sehgal et al. (1986) mapped IFNB2 to chromosome 7 by means of a cDNA clone in blot-hybridization experiments on DNA from a panel of human-rodent somatic cell hybrids. Zilberstein et al. (1986) cloned cDNA for the 1.3-kb RNA designated IFNB2. Expression studies showed that the IFN-beta-2 secreted by DNA-transformed rodent cells is a processed 21-kD protein whose activity is cross-neutralized by antibodies to human IFN-beta-1 but not to

alpha or gamma interferon. The biologic significance of IFN-beta-2 lies in the fact that it is induced under conditions in which IFN-beta-1 is not induced, as in metabolically stressed cells. Its induction by IL1 (OMIM Ref. No. 147720) and TNF (OMIM Ref. No. 191160) suggests that it may play a role as an autocrine mediator of some effects of these cytokines in inflammation and acute phase responses, as well as regulate cell proliferation. As discussed by Sehgal et al. (1987), IFNB2 is identical to B-cell differentiation factor (BSF2) and enhances proliferation in hybridoma/plasmacytoma cells. Hirano et al. (1986) reported the molecular cloning, structural analysis, and functional expression of cDNA encoding human BSF2. The primary sequence of BSF2 deduced from the cDNA shows that it has 184 amino acids and is distinct from other interleukins. In addition to its antiviral activity, beta-2 interferon elicits acute phase response in liver cells and is identical to hepatocyte stimulatory factor. It also is identical to hybridoma growth factor A subset of plasmacytoma (PCT), designated extramedullary PCT, is distinguished from multiple myeloma and solitary PCT of bone by its distribution among various tissue sites but not bone marrow. Extramedullary (extraosseous) PCTs are rare sponta-

neous neoplasms of mice but are readily induced in a susceptible strain, BALB/c, by treatment with pristane. The tumors develop in peritoneal granulomas and are characterized by Myc-activating t(12;15) chromosomal translocations and, most frequently, by secretion of IgA. To test directly the contribution of IL6 to PCT development, Kovalchuk et al. (2002) generated BALB/c mice carrying a widely expressed IL6 transgene. All mice exhibited lymphoproliferation and plasmacytosis. By 18 months of age, more than half developed readily transplantable PCTs in lymph nodes, Peyer patches, and sometimes spleen.

These neoplasms also had the t(12;15) translocations, but remarkably, none expressed IgA. Approximately 30% of the mice developed follicular and diffuse large cell B-cell lymphomas that often coexisted with PCTs. These findings provided a unique model of extramedullary PCT for studies on pathogenesis and treatment and suggested a role for IL6 in the genesis of germinal center-derived lymphomas

[0448] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0449] Hirano, T.; Yasukawa, K.; Harada, H.; Taga, T.; Watanabe,

Y.; Matsuda, T.; Kashiwamura, S.; Nakajima, K.; Koyama, K.; Iwamatsu, A.; Tsunasawa, S.; Sakiyama, F.; Matsui, H.; Takahara, Y.; Taniguchi, T.; Kishimoto, T. : Complementary DNA for a novel human interleukin (BSF-2) that induces B lymphocytes to produce immunoglobulin. Nature 324: 73-76, 1986. ; and

[0450] Kovalchuk, A. L.; Kim, J. S.; Park, S. S.; Coleman, A. E.; Ward, J. M.; Morse, H. C, III; Kishimoto, T.; Potter, M.; Janz, S. : IL-6 transgenic mouse model for extraosseous plasmacytoma.

[0451] Further studies establishing the function and utilities of IL6 are found in John Hopkins OMIM database record ID 147620, and in cited publications numbered 528-55 and 554-558 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Lecithin Retinol Acyltransferase (phosphatidylcholine--retinol O-acyltransferase) (LRAT, Accession XM_011181) is another VGAM22 host target gene. LRAT BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LRAT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LRAT BINDING SITE,

designated SEQ ID:259, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0452] Another function of VGAM22 is therefore inhibition of Lecithin Retinol Acyltransferase (phosphatidylcholine--retinol O-acyltransferase) (LRAT, Accession XM_011181). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LRAT. Myosin Light Chain Kinase 2, Skeletal Muscle (MYLK2, Accession NM_033118) is another VGAM22 host target gene. MYLK2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MYLK2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MYLK2 BINDING SITE, designated SEQ ID:226, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0453] Another function of VGAM22 is therefore inhibition of Myosin Light Chain Kinase 2, Skeletal Muscle (MYLK2, Accession NM_033118). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and

clinical conditions associated with MYLK2. Protein Kinase, CAMP-dependent, Catalytic, Beta (PRKACB, Accession NM_002731) is another VGAM22 host target gene.

PRKACB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRKACB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRKACB BINDING SITE, designated SEQ ID:61, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0454] Another function of VGAM22 is therefore inhibition of Protein Kinase, CAMP-dependent, Catalytic, Beta (PRKACB, Accession NM_002731), a gene which is the catalytic beta subunit of cAMP-dependent protein kinase (PKA). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRKACB. The function of PRKACB has been established by previous studies. Most of the effects of cAMP in the eukaryotic cell are mediated through the phosphorylation of target proteins on serine or threonine residues by the cAMP-dependent protein kinase (EC 2.7.1.37). The inactive cAMP-dependent protein kinase is a tetramer

composed of 2 regulatory and 2 catalytic subunits. The cooperative binding of 4 molecules of cAMP dissociates the enzyme in a regulatory subunit dimer and 2 free active catalytic subunits. In the human, 4 different regulatory subunits (PRKAR1A, 188830; PRKAR1B, 176911; PRKAR2A, 176910; and PRKAR2B, 176912) and 3 catalytic subunits (PRKACA; PRKACB, 176892; and PRKACG 176893) have been identified. Animal model experiments lend further support to the function of PRKACB. The intracellular second messenger cAMP affects cell physiology by directly interacting with effector molecules that include cyclic nucleotide-gated ion channels, cAMP-regulated G protein exchange factors, and cAMP-dependent protein kinases (PKA). Two catalytic subunits, C-alpha (OMIM Ref. No. PRKACA) and C-beta (OMIM Ref. No. PRKACB), are expressed in the mouse and mediate the effects of PKA. Skalhogg et al. (2002) generated a null mutation in the major catalytic subunit of PKA, C-alpha, and observed early postnatal lethality in the majority of C-alpha knockout mice. Surprisingly, a small percentage of C-alpha knockout mice, although runted, survived to adulthood. This growth retardation was not due to decreased GH (OMIM Ref. No. 139250) production but did correlate with

a reduction in IGF1 (OMIM Ref. No. 147440) mRNA in the liver and diminished production of the major urinary proteins in kidney. In these animals, compensatory increases in C-beta levels occurred in brain whereas many tissues, including skeletal muscle, heart, and sperm, contained less than 10% of the normal PKA activity. Analysis of sperm in C-alpha knockout males revealed that spermatogenesis progressed normally but that mature sperm had defective forward motility

[0455] It is appreciated that the abovementioned animal model for PRKACB is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[0456] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0457] Skalhegg, B. S.; Huang, Y.; Su, T.; Idzerda, R. L.; McKnight, G. S.; Burton, K. A. : Mutation of the C-alpha subunit of PKA leads to growth retardation and sperm dysfunction. Molec. Endocr. 16: 630-639, 2002. ; and

[0458] Tasken, K.; Solberg, R.; Zhao, Y.; Hansson, V.; Jahnsen, T.; Siciliano, M. J. : The gene encoding the catalytic subunit C-alpha of cAMP-dependent protein kinase (locus

PRKACA) localize.

[0459] Further studies establishing the function and utilities of PRKACB are found in John Hopkins OMIM database record ID 176892, and in cited publications numbered 553 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Prolactin Receptor (PRLR, Accession NM_000949) is another VGAM22 host target gene. PRLR BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRLR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRLR BINDING SITE, designated SEQ ID:51, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0460] Another function of VGAM22 is therefore inhibition of Prolactin Receptor (PRLR, Accession NM_000949), a gene which is a receptor for the anterior pituitary hormone prolactin. Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRLR. The function of PRLR has been established by previous studies. Owerbach et al. (1981) did Southern blot analyses of DNA from human-mouse

cell hybrids to show that the prolactin gene is located on chromosome 6 (Owerbach et al., 1981). It bears homology to the genes for growth hormone (OMIM Ref. No. 139250) and chorionic somatomammotropin (OMIM Ref. No. 150200), which are on chromosome 17, but not as close homology as these two bear to each other (Cooke et al., 1981). Only 16% sequence homology of the growth hormone and prolactin gene has been found (Shome and Parlow, 1977). The regional assignment of prolactin is of interest because of possible association between prolactin-secreting adenomas and specific HLA alleles (Farid et al., 1980). Larrea et al. (1987) presented the results of family studies suggesting that there is a familial factor determining the occurrence of the 'big-big' form as the predominant immunoreactive PRL species in blood. By somatic cell hybridization, Taggart et al. (1987) narrowed the assignment of the PRL gene to 6pter-p21.1. Evans et al. (1988, 1989) mapped the prolactin gene in a series of overlapping deletions of chromosome 6 produced by gamma-irradiation of a human lymphoblastoid cell line followed by selection for HLA antigen-loss mutants. As pointed out by DiMattia (1998), the PRL gene possesses alternative tissue-specific promoters that are located 5,563 basepairs

apart. The 5-prime promoter is specific for expression of prolactin in the decidualized human endometrium and in lymphoblastoid cells such as the human cell line IM-9-P3; the downstream promoter is specific for expression in the pituitary lactotrope and is under the control of the POU-homeodomain transcription factor PIT1 (OMIM Ref. No. 173110). Transcriptional control of the nonpituitary start site is linked to the differentiation of the endometrial stromal cell into the decidual cell during the secretory phase of the ovulatory cycle (DiMattia et al., 1990, Gellersen et al., 1994). By deletion analysis of the human PRL promoter in endometrial stromal cells decidualized in vitro, Watanabe et al. (2001) demonstrated a 536-bp enhancer located between nucleotides -2040 and -1505 in the 5-prime-flanking region. DNase I footprint analysis of decidualized endometrial stromal cells revealed 3 protected regions, FP1-FP3. Transfection of overlapping 100-bp fragments of the 536-bp enhancer indicated that FP1 and FP3 each conferred enhancer activity. Gel shift assays indicated that both FP1 and FP3 bind AP1 (OMIM Ref. No. 165160), and that JUND (OMIM Ref. No. 165162) and FOSL2 (OMIM Ref. No. 601575) are components of the AP1 complex in decidual fibroblasts. Mutation of the AP1

binding site in either FP1 or FP3 decreased enhancer activity by approximately 50%, while mutation of both sites almost completely abolished activity

[0461] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0462] Watanabe, K.; Kessler, C. A.; Bachurski, C. J.; Kanda, Y.; Richardson, B. D.; Stanek, J.; Handwerger, S.; Brar, A. K. : Identification of a decidua-specific enhancer on the human prolactin gene with two critical activator protein 1 (AP-1) binding sites. *Molec. Endocr.* 15: 638-653, 2001. ; and

[0463] DiMattia, G. E.; Gellersen, B.; Duckworth, M. L.; Friesen, H. G. : Human prolactin gene expression: the use of an alternative noncoding exon in decidua and the IM-9-P3 lymphoblast cell.

[0464] Further studies establishing the function and utilities of PRLR are found in John Hopkins OMIM database record ID 176761, and in cited publications numbered 493-500 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Solute Carrier Family 6 (neurotransmitter transporter, taurine), Member 6 (SLC6A6, Accession NM_003043) is another VGAM22 host

target gene. SLC6A6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC6A6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC6A6 BINDING SITE, designated SEQ ID:65, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0465] Another function of VGAM22 is therefore inhibition of Solute Carrier Family 6 (neurotransmitter transporter, taurine), Member 6 (SLC6A6, Accession NM_003043), a gene which transports taurine and other beta-amino acids like beta-alanine. Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC6A6. The function of SLC6A6 has been established by previous studies. Taurine (2-aminoethanesulfonic acid) is a major intracellular amino acid in mammals. It is involved in a number of important physiologic processes, including bile acid conjugation in hepatocytes, modulation of calcium flux and neural excitability, osmoregulation, detoxification, and membrane stabilization. The cells of most organisms respond to hypertonicity by the intracellular accumulation of

high concentrations of small organic solutes (osmolytes) that, in contrast to high concentrations of electrolytes, do not perturb the function of macromolecules. The renal medulla is normally the only tissue in mammals that undergoes wide shifts in tonicity. Its hypertonicity when the kidney is excreting a concentrated urine is fundamental to water conservation. The taurine content of the renal medulla of rats infused with 5% NaCl is higher than that in controls, suggesting that taurine behaves as an osmolyte in the renal medulla. Indeed, taurine functions as an osmolyte in Madin–Darby canine kidney (MDCK) cells. When MDCK cells cultured in isotonic medium are switched to hypertonic medium, their content of taurine doubles through the taking up of taurine from the medium. Taurine transport in these cells is dependent on sodium and chloride ions and is localized primarily in the basolateral plasma membrane. Uchida et al. (1992) cloned the cDNA for the taurine transporter in MDCK cells. The sequence of the cDNA indicated that the taurine transporter has considerable amino acid sequence similarity to previously cloned Na(+)- and Cl(-)-dependent transporters. Northern hybridization indicated that the quantity of mRNA for the taurine transporter in MDCK cells is regulated by hyper-

tonicity. Furthermore, the Northern hybridizations indicated that the taurine transporter is present also in ileal mucosa, brain, liver, and heart.

[0466] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0467] Ramamoorthy, S.; Leibach, F. H.; Mahesh, V. B.; Han, H.; Yang-Feng, T.; Blakely, R. D.; Ganapathy, V. : Functional characterization and chromosomal localization of a cloned taurine transporter from human placenta. *Biochem. J.* 300: 893–900, 1994. ; and

[0468] Uchida, S.; Kwon, H. M.; Yamauchi, A.; Preston, A. S.; Marumo, F.; Handler, J. S. : Molecular cloning of the cDNA for an MDCK cell Na(+)- and Cl(-)-dependent taurine transporter that is r.

[0469] Further studies establishing the function and utilities of SLC6A6 are found in John Hopkins OMIM database record ID 186854, and in cited publications numbered 263–265 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. WAS Protein Family, Member 3 (WASF3, Accession NM_006646) is another VGAM22 host target gene. WASF3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region

of mRNA encoded by WASF3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WASF3 BINDING SITE, designated SEQ ID:109, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0470] Another function of VGAM22 is therefore inhibition of WAS Protein Family, Member 3 (WASF3, Accession NM_006646), a gene which stimulates actin polymerization. Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WASF3. The function of WASF3 has been established by previous studies. The actin cytoskeleton plays critical roles in cell morphologic changes and motility. Rho family small GTPases such as Rho (see OMIM Ref. No. 165370), RAC (see OMIM Ref. No. 602048), and CDC42 (OMIM Ref. No. 116952) organize the actin cytoskeleton. Other major players in actin-based motility are the 7 members of the ARP2/3 complex (see OMIM Ref. No. 604221). The Wiskott-Aldrich syndrome protein (WASP; 301000) and WASP-like (WASL; 605056) are among the downstream effector molecules involved in the

transmission of signals from tyrosine kinase receptors and small GTPases to the actin cytoskeleton. WASF1 (OMIM Ref. No. 605035) is also involved in actin reorganization, but its expression is restricted to brain. By searching an EST database for homologs of WASF1 and by screening cDNA libraries, Suetsugu et al. (1999) identified WASF2 (OMIM Ref. No. 605068) and WASF3, which they termed WAVE2 and WAVE3, respectively. The predicted 502-amino acid WASF3 protein shares 48% amino acid identity with WASF1. Northern blot analysis revealed that, like WASF1, WASF3 expression is strongest in brain, although weak expression was detected in kidney and liver. SDS-PAGE analysis showed that, like other WASP family members, WASF3 binds actin through its C-terminal verprolin homology (VPH) domain. Immunofluorescence microscopy demonstrated that ectopically expressed WASF3 induces abnormal actin clusters. These actin cluster formations were suppressed by deletion of the VPH domain of WASF3.

[0471] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0472] Nagase, T.; Ishikawa, K.; Suyama, M.; Kikuno, R.; Hiro-

sawa, M.; Miyajima, N.; Tanaka, A.; Kotani, H.; Nomura, N.; Ohara, O. : Prediction of the coding sequences of unidentified human genes. XII. The complete sequences of 100 new cDNA clones from brain which code for large proteins in vitro. DNA Res. 5: 355–364, 1998. ; and

[0473] Suetsugu, S.; Miki, H.; Takenawa, T. : Identification of two human WAVE/SCAR homologues as general actin regulatory molecules which associate with the Arp2/3 complex. Biochem. Biophys.

[0474] Further studies establishing the function and utilities of WASF3 are found in John Hopkins OMIM database record ID 605068, and in cited publications numbered 21 and 287 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Kell Blood Group Precursor (McLeod phenotype) (XK, Accession NM_021083) is another VGAM22 host target gene. XK BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by XK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of XK BINDING SITE, designated SEQ ID:181, to the nucleotide sequence of VGAM22 RNA, herein designated

VGAM RNA, also designated SEQ ID:23.

[0475] Another function of VGAM22 is therefore inhibition of Kell Blood Group Precursor (McLeod phenotype) (XK, Accession NM_021083). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with XK. Zyxin (ZYG, Accession NM_003461) is another VGAM22 host target gene. ZYG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZYG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZYG BINDING SITE, designated SEQ ID:69, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0476] Another function of VGAM22 is therefore inhibition of Zyxin (ZYG, Accession NM_003461). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZYG. Ras Homolog Gene Family, Member F (in filopodia) (ARHF, Accession NM_019034) is another VGAM22 host target gene. ARHF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

ARHF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARHF BINDING SITE, designated SEQ ID:167, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0477] Another function of VGAM22 is therefore inhibition of Ras Homolog Gene Family, Member F (in filopodia) (ARHF, Accession NM_019034). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARHF. Discoidin Domain Receptor Family, Member 1 (DDR1, Accession NM_001954) is another VGAM22 host target gene. DDR1 BINDING SITE1 through DDR1 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by DDR1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DDR1 BINDING SITE1 through DDR1 BINDING SITE3, designated SEQ ID:57, SEQ ID:122 and SEQ ID:123 respectively, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0478] Another function of VGAM22 is therefore inhibition of Discoidin Domain Receptor Family, Member 1 (DDR1, Accession NM_001954). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DDR1. DKFZP547E1010 (Accession XM_040002) is another VGAM22 host target gene. DKFZP547E1010 BINDING SITE1 and DKFZP547E1010 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by DKFZP547E1010, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP547E1010 BINDING SITE1 and DKFZP547E1010 BINDING SITE2, designated SEQ ID:280 and SEQ ID:197 respectively, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0479] Another function of VGAM22 is therefore inhibition of DKFZP547E1010 (Accession XM_040002). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP547E1010. FLJ12650 (Accession NM_024522) is another VGAM22 host target gene. FLJ12650 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12650, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12650 BINDING SITE, designated SEQ ID:196, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0480] Another function of VGAM22 is therefore inhibition of FLJ12650 (Accession NM_024522). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12650. FLJ13265 (Accession NM_024877) is another VGAM22 host target gene. FLJ13265 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13265, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13265 BINDING SITE, designated SEQ ID:201, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0481] Another function of VGAM22 is therefore inhibition of

FLJ13265 (Accession NM_024877). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13265. FLJ20546 (Accession NM_017872) is another VGAM22 host target gene. FLJ20546 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20546, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20546 BINDING SITE, designated SEQ ID:155, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0482] Another function of VGAM22 is therefore inhibition of FLJ20546 (Accession NM_017872). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20546. FLJ32865 (Accession NM_144613) is another VGAM22 host target gene. FLJ32865 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ32865, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of FLJ32865 BINDING SITE, designated SEQ ID:251, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0483] Another function of VGAM22 is therefore inhibition of FLJ32865 (Accession NM_144613). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ32865. G-protein Coupled Receptor 88 (GPR88, Accession NM_022049) is another VGAM22 host target gene. GPR88 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GPR88, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GPR88 BINDING SITE, designated SEQ ID:185, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0484] Another function of VGAM22 is therefore inhibition of G-protein Coupled Receptor 88 (GPR88, Accession NM_022049). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GPR88. HSPC216 (Accession

NM_016478) is another VGAM22 host target gene.

HSPC216 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HSPC216, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSPC216 BINDING SITE, designated SEQ ID:149, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0485] Another function of VGAM22 is therefore inhibition of HSPC216 (Accession NM_016478). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSPC216. JIK (Accession NM_016281) is another VGAM22 host target gene. JIK BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by JIK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of JIK BINDING SITE, designated SEQ ID:148, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0486] Another function of VGAM22 is therefore inhibition of JIK

(Accession NM_016281). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with JIK. KIAA0153 (Accession NM_015140) is another VGAM22 host target gene. KIAA0153 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0153, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0153 BINDING SITE, designated SEQ ID:139, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0487] Another function of VGAM22 is therefore inhibition of KIAA0153 (Accession NM_015140). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0153. KIAA0215 (Accession NM_014735) is another VGAM22 host target gene. KIAA0215 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0215, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

KIAA0215 BINDING SITE, designated SEQ ID:130, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0488] Another function of VGAM22 is therefore inhibition of KIAA0215 (Accession NM_014735). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0215. KIAA0461 (Accession XM_047883) is another VGAM22 host target gene. KIAA0461 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0461, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0461 BINDING SITE, designated SEQ ID:291, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0489] Another function of VGAM22 is therefore inhibition of KIAA0461 (Accession XM_047883). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0461. MEGF10 (Accession NM_032446) is another VGAM22 host target gene. MEGF10 BINDING SITE is HOST

TARGET binding site found in the 3' untranslated region of mRNA encoded by MEGF10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MEGF10 BINDING SITE, designated SEQ ID:216, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0490] Another function of VGAM22 is therefore inhibition of MEGF10 (Accession NM_032446). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MEGF10. MGC2452 (Accession NM_032644) is another VGAM22 host target gene. MGC2452 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC2452, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC2452 BINDING SITE, designated SEQ ID:218, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0491] Another function of VGAM22 is therefore inhibition of

MGC2452 (Accession NM_032644). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC2452. MGC4796 (Accession XM_029031) is another VGAM22 host target gene. MGC4796 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC4796, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC4796 BINDING SITE, designated SEQ ID:266, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0492] Another function of VGAM22 is therefore inhibition of MGC4796 (Accession XM_029031). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC4796. Mitochondrial Ribosomal Protein L10 (MRPL10, Accession NM_145255) is another VGAM22 host target gene. MRPL10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MRPL10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of MRPL10 BINDING SITE, designated SEQ ID:256, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0493] Another function of VGAM22 is therefore inhibition of Mitochondrial Ribosomal Protein L10 (MRPL10, Accession NM_145255). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MRPL10. Mitochondrial Ribosomal Protein L42 (MRPL42, Accession XM_052542) is another VGAM22 host target gene. MRPL42 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MRPL42, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MRPL42 BINDING SITE, designated SEQ ID:299, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0494] Another function of VGAM22 is therefore inhibition of Mitochondrial Ribosomal Protein L42 (MRPL42, Accession XM_052542). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical

conditions associated with MRPL42. POLYDOM (Accession NM_024500) is another VGAM22 host target gene. POLYDOM BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by POLYDOM, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of POLYDOM BINDING SITE, designated SEQ ID:195, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0495] Another function of VGAM22 is therefore inhibition of POLYDOM (Accession NM_024500). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with POLYDOM. PRO0246 (Accession NM_014123) is another VGAM22 host target gene. PRO0246 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PRO0246, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO0246 BINDING SITE, designated SEQ ID:126, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also des-

ignated SEQ ID:23.

[0496] Another function of VGAM22 is therefore inhibition of PRO0246 (Accession NM_014123). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO0246. Smith–Magenis Syndrome Chromosome Region, Candidate 7 (SMCR7, Accession NM_139162) is another VGAM22 host target gene. SMCR7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SMCR7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SMCR7 BINDING SITE, designated SEQ ID:247, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0497] Another function of VGAM22 is therefore inhibition of Smith–Magenis Syndrome Chromosome Region, Candidate 7 (SMCR7, Accession NM_139162). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SMCR7. Tumor Protein D52 (TPD52, Accession NM_005079) is another VGAM22 host target gene. TPD52 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TPD52, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TPD52 BINDING SITE, designated SEQ ID:88, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0498] Another function of VGAM22 is therefore inhibition of Tumor Protein D52 (TPD52, Accession NM_005079). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TPD52. Zinc Finger Protein 384 (ZNF384, Accession NM_133476) is another VGAM22 host target gene. ZNF384 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF384, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF384 BINDING SITE, designated SEQ ID:239, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0499] Another function of VGAM22 is therefore inhibition of Zinc

Finger Protein 384 (ZNF384, Accession NM_133476). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF384. LOC124216 (Accession XM_058783) is another VGAM22 host target gene.

LOC124216 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC124216, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC124216 BINDING SITE, designated SEQ ID:307, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0500] Another function of VGAM22 is therefore inhibition of LOC124216 (Accession XM_058783). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC124216. LOC144509 (Accession XM_084882) is another VGAM22 host target gene. LOC144509 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC144509, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144509 BINDING SITE, designated SEQ ID:320, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0501] Another function of VGAM22 is therefore inhibition of LOC144509 (Accession XM_084882). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144509. LOC146822 (Accession XM_085606) is another VGAM22 host target gene. LOC146822 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146822, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146822 BINDING SITE, designated SEQ ID:324, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0502] Another function of VGAM22 is therefore inhibition of LOC146822 (Accession XM_085606). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC146822. LOC148371 (Accession XM_086164) is another VGAM22 host target gene. LOC148371 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC148371, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148371 BINDING SITE, designated SEQ ID:330, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0503] Another function of VGAM22 is therefore inhibition of LOC148371 (Accession XM_086164). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148371. LOC149373 (Accession XM_086507) is another VGAM22 host target gene. LOC149373 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149373, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149373 BINDING SITE, designated SEQ ID:333, to the nucleotide sequence of VGAM22 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:23.

[0504] Another function of VGAM22 is therefore inhibition of LOC149373 (Accession XM_086507). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149373. LOC151146 (Accession XM_087106) is another VGAM22 host target gene. LOC151146 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC151146, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151146 BINDING SITE, designated SEQ ID:336, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0505] Another function of VGAM22 is therefore inhibition of LOC151146 (Accession XM_087106). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151146. LOC157562 (Accession XM_098779) is another VGAM22 host target gene. LOC157562 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC157562, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157562 BINDING SITE, designated SEQ ID:357, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0506] Another function of VGAM22 is therefore inhibition of LOC157562 (Accession XM_098779). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157562. LOC160897 (Accession XM_090573) is another VGAM22 host target gene. LOC160897 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC160897, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC160897 BINDING SITE, designated SEQ ID:341, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0507] Another function of VGAM22 is therefore inhibition of LOC160897 (Accession XM_090573). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC160897. LOC161589 (Accession XM_090991) is another VGAM22 host target gene. LOC161589 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC161589, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC161589 BINDING SITE, designated SEQ ID:343, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0508] Another function of VGAM22 is therefore inhibition of LOC161589 (Accession XM_090991). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC161589. LOC163682 (Accession XM_099402) is another VGAM22 host target gene. LOC163682 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC163682, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC163682 BINDING SITE, designated SEQ ID:361, to

the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0509] Another function of VGAM22 is therefore inhibition of LOC163682 (Accession XM_099402). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC163682. LOC199692 (Accession NM_145295) is another VGAM22 host target gene. LOC199692 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC199692, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC199692 BINDING SITE, designated SEQ ID:257, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0510] Another function of VGAM22 is therefore inhibition of LOC199692 (Accession NM_145295). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC199692. LOC202108 (Accession XM_114442) is another VGAM22 host target gene. LOC202108 BINDING SITE is HOST TARGET binding site found in the 5' un-

translated region of mRNA encoded by LOC202108, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC202108 BINDING SITE, designated SEQ ID:367, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0511] Another function of VGAM22 is therefore inhibition of LOC202108 (Accession XM_114442). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC202108. LOC221468 (Accession NM_145316) is another VGAM22 host target gene. LOC221468 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221468, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221468 BINDING SITE, designated SEQ ID:258, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0512] Another function of VGAM22 is therefore inhibition of LOC221468 (Accession NM_145316). Accordingly, utilities

of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221468. LOC221838 (Accession XM_166521) is another VGAM22 host target gene. LOC221838 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC221838, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221838 BINDING SITE, designated SEQ ID:385, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0513] Another function of VGAM22 is therefore inhibition of LOC221838 (Accession XM_166521). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221838. LOC221839 (Accession XM_166506) is another VGAM22 host target gene. LOC221839 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC221839, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC221839 BINDING SITE, designated SEQ ID:384, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0514] Another function of VGAM22 is therefore inhibition of LOC221839 (Accession XM_166506). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221839. LOC90313 (Accession XM_030852) is another VGAM22 host target gene. LOC90313 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC90313, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90313 BINDING SITE, designated SEQ ID:268, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0515] Another function of VGAM22 is therefore inhibition of LOC90313 (Accession XM_030852). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90313. LOC92399 (Accession NM_138777) is another VGAM22 host target gene. LOC92399 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92399, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92399 BINDING SITE, designated SEQ ID:242, to the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, also designated SEQ ID:23.

[0516] Another function of VGAM22 is therefore inhibition of LOC92399 (Accession NM_138777). Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92399. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 23 (VGAM23) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0517] VGAM23 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM23 was detected is described hereinabove with reference to Figs. 1-8.

[0518] VGAM23 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Immunodeficiency Virus 1. VGAM23 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0519] VGAM23 gene encodes a VGAM23 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM23 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM23 precursor RNA is designated SEQ ID:9, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:9 is located at position 5531 relative to the genome of Human Immunodeficiency Virus 1.

[0520] VGAM23 precursor RNA folds onto itself, forming VGAM23 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide

sequence of the second half thereof.

[0521] An enzyme complex designated DICER COMPLEX, `dices` the VGAM23 folded precursor RNA into VGAM23 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 69%) nucleotide sequence of VGAM23 RNA is designated SEQ ID:24, and is provided hereinbelow with reference to the sequence listing part.

[0522] VGAM23 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM23 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM23 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[0523] VGAM23 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM23 host target RNA,

herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM23 RNA is an accurate or a partial inverted-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM23 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM23 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[0524] The complementary binding of VGAM23 RNA, herein designated VGAM RNA, to host target binding sites on VGAM23 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM23 host tar-

get RNA into VGAM23 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0525] It is appreciated that VGAM23 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM23 host target genes. The mRNA of each one of this plurality of VGAM23 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM23 RNA, herein designated VGAM RNA, and which when bound by VGAM23 RNA causes inhibition of translation of respective one or more VGAM23 host target proteins.

[0526] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM23 gene, herein designated VGAM GENE, on one or more VGAM23 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and

Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[0527] It is yet further appreciated that a function of VGAM23 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of viral infection by Human Immunodeficiency Virus 1. Specific functions, and accordingly utilities, of VGAM23 correlate with, and may be deduced from, the identity of the host target genes which VGAM23 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0528] Nucleotide sequences of the VGAM23 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM23 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM23 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM23 are further described hereinbelow with reference to Table 1.

[0529] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM23 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM23 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0530] As mentioned hereinabove with reference to Fig. 1, a function of VGAM23 gene, herein designated VGAM is inhibition of expression of VGAM23 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM23 correlate with, and may be deduced from, the identity of the target genes which VGAM23 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[0531] A Disintegrin and Metalloproteinase Domain 8 (ADAM8, Accession NM_001109) is a VGAM23 host target gene. ADAM8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADAM8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADAM8 BINDING SITE, designated SEQ ID:52,

to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0532] A function of VGAM23 is therefore inhibition of A Disintegrin and Metalloproteinase Domain 8 (ADAM8, Accession NM_001109). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADAM8. BN51 (BHK21) Temperature Sensitivity Complementing (BN51T, Accession XM_113557) is another VGAM23 host target gene. BN51T BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BN51T, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BN51T BINDING SITE, designated SEQ ID:363, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0533] Another function of VGAM23 is therefore inhibition of BN51 (BHK21) Temperature Sensitivity Complementing (BN51T, Accession XM_113557), a gene which complements a temperature-sensitive cell cycle mutation in BHK cells. Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical condi-

tions associated with BN51T. The function of BN51T has been established by previous studies. Two temperature-sensitive mutants have been isolated from the BHK-21 Syrian hamster cell line. Both of the human genes that complement these mutations, designated ts11 and tsBN51, lead to a block in progression through the G1 phase of the cell cycle at nonpermissive temperatures. Ts11 has been identified as asparagine synthetase; see 108370. The tsBN51 gene encodes a highly charged novel protein of 395 amino acids (Ittmann et al., 1987) whose biochemical function had not yet been determined when Greco et al. (1989) assigned the gene to 8q21 by study of rodent-human hybrid cells and by in situ hybridization using a tsBN51 probe. This is one of a considerable number of temperature-sensitive mutants which have been mapped to various autosomes and in several instances to the X chromosome.

[0534] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0535] Ittmann, M.; Greco, A.; Basilico, C. : Isolation of the human gene that complements a temperature-sensitive cell cycle mutation in BHK cells. *Molec. Cell. Biol.* 7: 3386-3393,

1987. ; and

[0536] Greco, A.; Ittmann, M.; Barletta, C.; Basilico, C.; Croce, C. M.; Cannizzaro, L. A.; Huebner, K. : Chromosomal localization of human genes required for G(1) progression in mammalian cell.

[0537] Further studies establishing the function and utilities of BN51T are found in John Hopkins OMIM database record ID 187280, and in cited publications numbered 625–626 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. CD3Z Antigen, Zeta Polypeptide (TiT3 complex) (CD3Z, Accession NM_000734) is another VGAM23 host target gene. CD3Z BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CD3Z, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CD3Z BINDING SITE, designated SEQ ID:48, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0538] Another function of VGAM23 is therefore inhibition of CD3Z Antigen, Zeta Polypeptide (TiT3 complex) (CD3Z, Accession NM_000734), a gene which may involve in as–

sembly and expression of the tcr complex as well as signal transduction upon antigen triggering. Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CD3Z. The function of CD3Z has been established by previous studies. Alarcon et al. (1988) described 2 brothers who had a low expression of antigen receptor on the surface of their T lymphocytes. Functional analyses of their T cells showed impaired immune response to alloantigens, tetanus toxoid, and mitogens. Biochemical studies showed reduced intracellular expression of CD3-zeta chains; all other components of the T-cell receptor-CD3 complex were expressed normally. Alarcon et al. (1988) suggested that the impaired association of the CD3-zeta chain with the other chains of the complex was the primary defect leading to the low expression of T-cell receptor-CD3 complex and immunodeficiency in these children. Failure to thrive had been diagnosed in the proband at 11 months; subsequently, chronic anorexia, diarrhea, and recurrent episodes of bronchopneumonia were noted. The diarrhea was shown to be associated with a malabsorption syndrome, which was unresponsive to a gluten-free diet. Biopsy of the small bowel showed ab-

sence of villi; however, the patient was negative for HLA-DR3 and -DR7. The boy died of severe autoimmune hemolytic anemia at the age of 3 years. The patient's brother had required hospital admission for respiratory infection, but on the whole was much more mildly affected than his brother. Animal model experiments lend further support to the function of CD3Z. Class I MHC molecules, known to be important for immune responses to antigen, are expressed also by neurons that undergo activity-dependent, long-term structural and synaptic modifications. Huh et al. (2000) showed that in mice genetically deficient for cell surface class I MHC, due to deletion of either TAP1 (OMIM Ref. No. 170260) or beta-2-microglobulin (OMIM Ref. No. 109700), or for the class I MHC receptor component CD3Z, refinement of connections between retina and central targets during development is incomplete. In the hippocampus of adult mutants, N-methyl-D-aspartate receptor-dependent long-term potentiation is enhanced, and long-term depression is absent. Specific class I MHC mRNAs are expressed by distinct mosaics of neurons, reflecting a potential for diverse neuronal functions. These results demonstrated an important role for these molecules in the activity-dependent

remodeling and plasticity of connections in the developing and mature mammalian central nervous system.

[0539] It is appreciated that the abovementioned animal model for CD3Z is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[0540] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0541] Huh, G. S.; Boulanger, L. M.; Du, H.; Riquelme, P. A.; Brotz, T. M.; Shatz, C. J. : Functional requirement for class I MHC in CNS development and plasticity. Science 290: 2155–2159, 2000. ; and

[0542] Alarcon, B.; Regueiro, J. R.; Arnaiz–Villena, A.; Terhorst, C. : Familial defect in the surface expression of the T–cell receptor–CD3 complex. New Eng. J. Med. 319: 1203–1208, 1988.

[0543] Further studies establishing the function and utilities of CD3Z are found in John Hopkins OMIM database record ID 186780, and in cited publications numbered 255–258, 60, 25 and 522–262 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Dishevelled Associated Activator of Morphogenesis 2

(DAAM2, Accession XM_166434) is another VGAM23 host target gene. DAAM2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DAAM2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DAAM2 BINDING SITE, designated SEQ ID:381, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0544] Another function of VGAM23 is therefore inhibition of Dishevelled Associated Activator of Morphogenesis 2 (DAAM2, Accession XM_166434), a gene which controls cell polarity and movement during development. Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DAAM2. The function of DAAM2 has been established by previous studies. By sequencing randomly selected cDNAs corresponding to relatively long transcripts from brain, Nagase et al. (1997) identified a cDNA which they designated KIAA0381. The KIAA0381 cDNA encodes an 864-amino acid protein predicted to be involved in cell division. RT-PCR analysis detected expression of KIAA0381 in most tissues tested. Wnt (see OMIM

Ref. No. 164975) signaling via the frizzled receptor (Fz; OMIM Ref. No. 600667) controls cell polarity and movement during development. Habas et al. (2001) reported that in human cells and during *Xenopus* embryogenesis, Wnt/Fz signaling activates the small GTPase Rho (OMIM Ref. No. 165390), a key regulator of cytoskeleton architecture. Wnt/Fz activation of Rho requires the cytoplasmic protein dishevelled (DVL; OMIM Ref. No. 601365) and a novel formin (see OMIM Ref. No. 136535) homology (FH) protein that they identified and named DAAM1 (OMIM Ref. No. 606626). Habas et al. (2001) identified DAAM2, which is identical to KIAA0381, as a protein that is closely related to DAAM1.

[0545] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0546] Habas, R.; Kato, Y.; He, X. : Wnt/Frizzled activation of Rho regulates vertebrate gastrulation and requires a novel Formin homology protein Daam1. *Cell* 107: 843–854, 2001. ; and

[0547] Nagase, T.; Ishikawa, K.; Nakajima, D.; Ohira, M.; Seki, N.; Miyajima, N.; Tanaka, A.; Kotani, H.; Nomura, N.; Ohara, O. : Prediction of the coding sequences of unidentified

human gene.

[0548] Further studies establishing the function and utilities of DAAM2 are found in John Hopkins OMIM database record ID 606627, and in cited publications numbered 206 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Discs, Large (Drosophila) Homolog 4 (DLG4, Accession NM_001365) is another VGAM23 host target gene. DLG4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DLG4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DLG4 BINDING SITE, designated SEQ ID:54, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0549] Another function of VGAM23 is therefore inhibition of Discs, Large (Drosophila) Homolog 4 (DLG4, Accession NM_001365), a gene which is a membrane-associated guanylate kinase and may intervene in synaptogenesis. Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DLG4. The function of DLG4 has been es-

established by previous studies. Neuregulins and their receptors, the ERBB protein tyrosine kinases, are essential for neuronal development, but their functions in the adult central nervous system are unknown. Huang et al. (2000) reported that ERBB4 (OMIM Ref. No. 600543) is enriched in the postsynaptic density and associates with PSD95. Heterologous expression of PSD95 enhanced NRG (OMIM Ref. No. 142445) activation of ERBB4 and MAP kinase (see OMIM Ref. No. 176948). Conversely, inhibiting expression of PSD95 in neurons attenuated NRG-mediated activation of MAP kinase. PSD95 formed a ternary complex with 2 molecules of ERBB4, suggesting that PSD95 facilitates ERBB4 dimerization. Finally, NRG suppressed induction of long-term potentiation in the hippocampal CA1 region without affecting basal synaptic transmission. Thus, NRG signaling may be synaptic and regulated by PSD95. Huang et al. (2000) concluded that a role of NRG signaling in the adult central nervous system may be modulation of synaptic plasticity. El-Husseini et al. (2002) identified palmitate cycling on PSD95 at the synapse and found that palmitate turnover on PSD95 is regulated by glutamate receptor activity. Acutely blocking palmitoylation dispersed synaptic clusters of PSD95 and caused a selective loss of

synaptic AMPA receptors (e.g., GRIA1; 138248). The authors also found that rapid glutamate-mediated AMPA receptor internalization requires depalmitoylation of PSD95. In a nonneuronal model system, clustering of PSD95, stargazin (OMIM Ref. No. 602911), and AMPA receptors was also regulated by ongoing palmitoylation of PSD95 at the plasma membrane. El-Husseini et al. (2002) concluded that palmitate cycling on PSD95 can regulate synaptic strength and activity-dependent plasticity.

[0550] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0551] Huang, Y. Z.; Won, S.; Ali, D. W.; Wang, Q.; Tanowitz, M.; Du, Q. S.; Pelkey, K. A.; Yang, D. J.; Xiong, W. C.; Salter, M. W.; Mei, L. : Regulation of neuregulin signaling by PSD-95 interacting with ErbB4 at CNS synapses. Neuron 26: 443-455, 2000. ; and

[0552] El-Husseini, A. E.-D.; Schnell, E.; Dakoji, S.; Sweeney, N.; Zhou, Q.; Prange, O.; Gauthier-Campbell, C.; Aguilera-Moreno, A.; Nicoll, R. A.; Brecht, D. S. : Synaptic strength regulated.

[0553] Further studies establishing the function and utilities of DLG4 are found in John Hopkins OMIM database record ID

602887, and in cited publications numbered 243–24 and 603–250 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Dystrophin (muscular dystrophy, Duchenne and Becker types) (DMD, Accession NM_004013) is another VGAM23 host target gene. DMD BINDING SITE1 through DMD BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by DMD, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DMD BINDING SITE1 through DMD BINDING SITE3, designated SEQ ID:73, SEQ ID:74 and SEQ ID:75 respectively, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0554] Another function of VGAM23 is therefore inhibition of Dystrophin (muscular dystrophy, Duchenne and Becker types) (DMD, Accession NM_004013), a gene which muscular dystrophy . Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DMD. The function of DMD has been established by previous studies. Roberts et al. (1992) described a general approach to the identification

of the basic defect in the one-third of DMD patients who do not show a gross rearrangement of the dystrophin gene. The method involved nested amplification, chemical mismatched detection, and sequencing of reverse transcripts of trace amounts of dystrophin mRNA from peripheral blood lymphocytes. Analysis of the entire coding region (11 kb) in 7 patients resulted in detection of a sequence change in each case that was clearly sufficient to cause the disease. All the mutations were expected to cause premature translation termination, and the resulting phenotypes were thus equivalent to those caused by frameshifting deletions; see 300377.0003–300377.0009. Deletions and point mutations in the DMD gene cause either DMD or the milder Becker muscular dystrophy, depending on whether the translational reading frame is lost or maintained. De Angelis et al. (2002) reasoned that because internal in-frame deletions in the protein produce only mild myopathic symptoms, a partially corrected phenotype could be restored by preventing the inclusion of specific mutated exons in the mature dystrophin mRNA. Such control had previously been accomplished by the use of synthetic oligonucleotides. To circumvent the disadvantageous necessity for periodic administration of the

synthetic oligonucleotides, De Angelis et al. (2002) produced several constructs able to express in vivo, in a stable fashion, large amounts of chimeric RNAs containing antisense sequences. They showed that antisense molecules against exon 51 splice junctions were able to direct skipping of that exon in the human DMD deletion 48–50 and to rescue dystrophin synthesis. They also showed that the highest skipping activity occurred when antisense constructs against the 5–prime and 3–prime splice sites were coexpressed in the same cell. The effects were tested in cultured myoblasts from a DMD patient. The deletion of exons 48–50 resulted in a premature termination codon in exon 51. The antisense sequences complementary to exon 51 splice junctions induced efficient skipping of exon 51 and partial rescue of dystrophin synthesis. X-linked dilated cardiomyopathy is a dystrophinopathy characterized by severe cardiomyopathy with no skeletal muscle involvement. Several XLCM patients have been described with mutations that abolish dystrophin muscle isoform expression, but with increased expression of brain and cerebellar Purkinje isoforms of the gene exclusively in the skeletal muscle. Bastianutto et al. (2001) determined that 2 XLCM patients bore deletions

that removed the muscle promoter and exon 1, but not the brain and cerebellar Purkinje promoters. The brain and cerebellar Purkinje promoters were found to be essentially inactive in muscle cell lines and primary cultures. Since dystrophin muscle enhancer 1 (DME1), a muscle-specific enhancer, is preserved in these patients, the authors tested its ability to upregulate the brain and cerebellar Purkinje promoters in muscle cells. Brain and cerebellar Purkinje promoter activity was significantly increased in the presence of DME1, and activation was observed exclusively in cells presenting a skeletal muscle phenotype versus cardiomyocytes. The authors suggested a role for DME1 in the induction of brain and cerebellar Purkinje isoform expression in the skeletal muscle of XLCM patients defective for muscle isoform expression. Animal model experiments lend further support to the function of DMD. Using DNA microarray, Porter et al. (2002) established a molecular signature of dystrophinopathy in the mdx mouse. In leg muscle, 242 differentially expressed genes were identified. Data provided evidence for coordinated activity of numerous components of a chronic inflammatory response, including cytokine and chemokine signaling, leukocyte adhesion and

diapedesis, invasive cell type-specific markers, and complement system activation. Upregulation of secreted phosphoprotein 1 (SPP1; 166490) mRNA and protein in dystrophic muscle identified a novel linkage between inflammatory cells and repair processes. Extracellular matrix genes were upregulated in mdx to levels similar to those in DMD. Since, unlike DMD, mdx exhibits little fibrosis, data suggested that collagen regulation at post-transcriptional stages may mediate extensive fibrosis in DMD.

[0555] It is appreciated that the abovementioned animal model for DMD is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[0556] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0557] De Angelis, F. G.; Sthandier, O.; Berarducci, B.; Toso, S.; Galluzzi, G.; Ricci, E.; Cossu, G.; Bozzoni, I. : Chimeric snRNA molecules carrying antisense sequences against the splice junctions of exon 51 of the dystrophin pre-mRNA induce exon skipping and restoration of a dystrophin synthesis in delta-48-50 DMD cells. Proc Nat.

Acad. Sci. 99: 9456–9461, 2002. ; and

[0558] Bastianutto, C.; Bestard, J. A.; Lahnakoski, K.; Broere, D.; De Visser, M.; Zaccolo, M.; Pozzan, T.; Ferlini, A.; Muntoni, F.; Patarnello, T.; Klamut, H. J. : Dystrophin muscle enhance.

[0559] Further studies establishing the function and utilities of DMD are found in John Hopkins OMIM database record ID 300377, and in cited publications numbered 404–409, 411, 412–419, 327, 328, 420–425, 210, 332–337, 329, 338–343, 348–347, 349–353, 358, 355–357, 330, 359–360, 331, 361–370, 310, 371–379, 383–382, 384–385, 88–41, 311–31 and 42–43 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Emopamil Binding Protein (sterol isomerase) (EBP, Accession NM_006579) is another VGAM23 host target gene. EBP BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by EBP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EBP BINDING SITE, designated SEQ ID:108, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0560] Another function of VGAM23 is therefore inhibition of Emopamil Binding Protein (sterol isomerase) (EBP, Accession NM_006579), a gene which catalyzes the conversion of delta8-sterols to their corresponding delta7-isomers. Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EBP. The function of EBP has been established by previous studies. Because of the clinical similarities between X-linked dominant chondrodysplasia punctata-2 and CHILD syndrome (OMIM Ref. No. 308050), Grange et al. (2000) analyzed plasma sterols in a patient with typical CHILD syndrome. The levels of 8-dehydrocholesterol and 8(9)-cholestenol were increased in this patient to the same degree as in CDPX2 patients. The authors subsequently identified a nonsense mutation in exon 3 of the patient's 3-beta-hydroxysteroid-delta(8),delta(7)-isomerase gene. The authors suggested that at least some cases of CHILD syndrome are caused by 3-beta-hydroxysteroid-delta(8),delta(7)-isomerase deficiency and are allelic to CDPX2, although the almost exclusively unilateral distribution of abnormalities in CHILD syndrome versus the bilateral disease of CDPX2 remained

to be explained. Konig et al. (2002) stated that the association of CHILD syndrome with mutation in the EBP gene by Grange et al. (2000) was erroneous and was in fact a case of CDPX2 with predominantly unilateral involvement. Konig et al. (2002) pointed out that an X-linked dominant disorder usually showing an asymmetric involvement such as CDPX2 may give rise by way of exception to extreme lateralization, whereas the CHILD syndrome usually shows extreme lateralization but may exceptionally manifest itself in almost symmetrically arranged skin lesions. Animal model experiments lend further support to the function of EBP. 'Tattered' (Td) is an X-linked, semidominant mouse mutation associated with prenatal male lethality. Heterozygous females are small and at 4 to 5 days of age develop patches of hyperkeratotic skin where no hair grows, resulting in a striping of the coat in adults. Craniofacial anomalies and twisted toes have also been observed in some affected females. The phenotype of Td is similar to that seen in heterozygous human females with X-linked dominant chondrodysplasia punctata (CDPX2; 302960), as well as in another X-linked, semidominant mouse mutation, 'bare patches' (Bpa). The Bpa gene (NSDHL; 300275) was identified by Liu et al. (1999), who showed that it en-

codes a protein with homology to 3-beta-hydroxysteroid dehydrogenases that functions in one of the later steps of cholesterol biosynthesis. CDPX2 patients display skin defects including linear or whorled atrophic and pigmentary lesions, striated hyperkeratosis, coarse lusterless hair and alopecia, cataracts, and skeletal abnormalities including short stature, rhizomelic shortening of the limbs, epiphyseal stippling, and craniofacial defects. Derry et al. (1999) identified the defect in Td mice as a single amino acid substitution in the delta(8)-delta(7) sterol isomerase known as emopamil-binding protein (Ebp) and also identified alterations in human EBP in 7 unrelated CDPX2 patients.

[0561] It is appreciated that the abovementioned animal model for EBP is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[0562] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0563] Grange, D. K.; Kratz, L. E.; Braverman, N. E.; Kelley, R. I. : CHILD syndrome caused by deficiency of 3-beta-hydroxysteroid-delta-8,delta-7-isomerase. Am. J.

Med. Genet. 90: 328–335, 2000. ; and

[0564] Liu, X. Y.; Dangel, A. W.; Kelley, R. I.; Zhao, W.; Denny, P.; Botcherby, M.; Cattanach, B.; Peters, J.; Hunsicker, P. R.; Mallon, A.–M.; Strivens, M. A.; Bate, R.; Miller, W.; Rhodes.

[0565] Further studies establishing the function and utilities of EBP are found in John Hopkins OMIM database record ID 300205, and in cited publications numbered 442–451, 463–46 and 468 listed in the bibliography section herein–below, which are also hereby incorporated by reference. Fanconi Anemia, Complementation Group G (FANCG, Accession NM_004629) is another VGAM23 host target gene. FANCG BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FANCG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FANCG BINDING SITE, designated SEQ ID:85, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0566] Another function of VGAM23 is therefore inhibition of Fanconi Anemia, Complementation Group G (FANCG, Accession NM_004629). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and

clinical conditions associated with FANCG. FE65L2 (Accession NM_006051) is another VGAM23 host target gene. FE65L2 BINDING SITE1 through FE65L2 BINDING SITE4 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by FE65L2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FE65L2 BINDING SITE1 through FE65L2 BINDING SITE4, designated SEQ ID:99, SEQ ID:236, SEQ ID:237 and SEQ ID:238 respectively, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0567] Another function of VGAM23 is therefore inhibition of FE65L2 (Accession NM_006051), a gene which may modulate the internalization of beta-amyloid precursor protein. Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FE65L2. The function of FE65L2 has been established by previous studies. To identify genes similar to Fe65 (OMIM Ref. No. 602709), Duilio et al. (1998) screened a rat brain cDNA library and isolated a Fe65L2 cDNA encoding a deduced 504-amino acid polypeptide. Like Fe65 and Fe65L1 (OMIM Ref. No. 602710), the rat

Fe65L2 protein contains 2 phosphotyrosine-binding (PTB) domains and a WW domain. Northern blot analysis detected predominant expression of a 2-kb Fe65L2 mRNA in rat brain and testis. Using the rat cDNA fragment as probe, Tanahashi and Tabira (1999) cloned human Fe65L2 from a fetal brain cDNA library. Fe65L2 encodes a deduced 486-amino acid protein that shares 86% sequence identity with the rat protein. Using RT-PCR of human fetal brain mRNA, Tanahashi and Tabira (1999) also identified a variant, caused by the splicing of a 6-nucleotide mini-exon, that results results in a peptide lacking 2 amino acids in the first PTB domain. Northern blot analysis revealed expression of a 2.2-kb transcript expressed mainly in the brain and in all brain regions tested. A 2.9-kb transcript was found in other tissues, with strongest expression in pancreas. By radiation hybrid analysis, Tanahashi and Tabira (1999) mapped the FE65L2 gene to chromosome 5.

[0568] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0569] Duilio, A.; Faraonio, R.; Minopoli, G.; Zambrano, N.; Russo, T. : Fe65L2: a new member of the Fe65 protein family in-

teracting with the intracellular domain of the Alzheimer's beta-amyloid precursor protein. Biochem. J. 330: 513-519, 1998. ; and

[0570] Tanahashi, H.; Tabira, T. : Genome structure and chromosomal mapping of the gene for Fe65L2 interacting with Alzheimer's beta-amyloid precursor protein. Biochem. Biophys. Res. Commun. 25.

[0571] Further studies establishing the function and utilities of FE65L2 are found in John Hopkins OMIM database record ID 602711, and in cited publications numbered 47-49 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Fibroblast Growth Factor Receptor 4 (FGFR4, Accession NM_002011) is another VGAM23 host target gene. FGFR4 BINDING SITE1 and FGFR4 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by FGFR4, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FGFR4 BINDING SITE1 and FGFR4 BINDING SITE2, designated SEQ ID:58 and SEQ ID:55 respectively, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0572] Another function of VGAM23 is therefore inhibition of Fibroblast Growth Factor Receptor 4 (FGFR4, Accession NM_002011), a gene which receptor tyrosine kinase, preferentially binds acidic FGF. Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FGFR4. The function of FGFR4 has been established by previous studies. Partanen et al. (1991) reported the cDNA cloning and analysis of a novel member of the fibroblast growth factor receptor (FGFR) gene family expressed in K562 erythroleukemia cells. Its deduced amino acid sequence was 55% identical with the previously characterized FGFRs, FLG (FGFR1; 136350) and BEK (OMIM Ref. No. 176943), and had the structural characteristics of an FGFR family member including 3 immunoglobulin-like domains in its extracellular part. The expression pattern of FGFR4 was found to be distinct from that of FLG and BEK and also distinct from that of FGFR3 (OMIM Ref. No. 134934), which they (Keegan et al., 1991) had also cloned from K562 erythroleukemia cells. To elucidate further the physiologic relevance of protein-tyrosine kinases and to search for additional members of the gene family as possible factors in carcinogenesis, Holtrich et al. (1991) amplified mRNA

from lung tissue by the polymerase chain reaction (PCR) using PTK-specific primers followed by sequencing of the clones. They identified a novel protein-tyrosine kinase, which they called TKF (tyrosine kinase related to fibroblast growth factor receptor). Among a wide variety of cells and tissues tested, including human lymphocytes and macrophages, TKF was found to be expressed only in lung and in some tumors of lung origin as well as in malignancies not derived from lung tissues. Sequence comparison has demonstrated that TKF is identical to FGFR4 (Scott, 1999). By analysis of somatic cell hybrids and by in situ hybridization, Armstrong et al. (1992) mapped the FGFR4 gene to 5q33-qter, an area involved in leukemias and lymphomas. In a radiation hybrid mapping of 18 genes on distal 5q, Warrington et al. (1992) found that the FGFR4 gene lies distal to DRD1 with high probability. Assuming that the mapping of DRD1 is correct, FGFR4 would be located in the segment 5q35.1-qter. Using an interspecific backcross mapping panel, Avraham et al. (1994) mapped the Fgfr4 gene to mouse chromosome 13 in a region of homology of synteny with distal human 5q.

[0573] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [0574] Holtrich, U.; Brauninger, A.; Strebhardt, K.; Rubsamen-Waigmann, H. : Two additional protein-tyrosine kinases expressed in human lung: fourth member of the fibroblast growth factor receptor family and an intracellular protein-tyrosine kinase. *Proc. Nat. Acad. Sci.* 88: 10411-10415, 1991. ; and
- [0575] Avraham, K. B.; Givol, D.; Avivi, A.; Yayon, A.; Copeland, N. G.; Jenkins, N. A. : Mapping of murine fibroblast growth factor receptors refines regions of homology between mouse and huma.
- [0576] Further studies establishing the function and utilities of FGFR4 are found in John Hopkins OMIM database record ID 134935, and in cited publications numbered 196, 197-198, 61 and 199-203 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Gonadotropin-releasing Hormone Receptor (GNRHR, Accession NM_000406) is another VGAM23 host target gene. GNRHR BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by GNRHR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the

nucleotide sequences of GNRHR BINDING SITE, designated SEQ ID:38, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0577] Another function of VGAM23 is therefore inhibition of Gonadotropin-releasing Hormone Receptor (GNRHR, Accession NM_000406), a gene which stimulates the secretion-stimulates phosphoinositide turnover and membrane depolarization. Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GNRHR. The function of GNRHR has been established by previous studies. Kakar et al. (1992) isolated a cDNA for the GNRH receptor and showed that it encodes a protein with a transmembrane topology similar to that of other G protein-coupled 7-transmembrane-domain receptors. Grosse et al. (1997) used RT-PCR of human pituitary poly(A)+ RNA to clone the full-length GNRHR gene and a second truncated cDNA characterized by a 128-bp deletion between nucleotide positions 522 and 651. The deletion causes a frameshift in the open reading frame, thus generating new coding sequence for a further 75 amino acids. The truncated cDNA arises from alternative splicing that uses a cryptic 3-prime splice site in exon 2. Translation products of ap-

proximately 45 to 50 and 42 kD were immunoprecipitated from COS-7 cells transfected with wildtype and truncated GNRHR cDNAs, respectively. The splice variant was incapable of ligand binding and signal transduction. Coexpression of wildtype and truncated proteins in transiently or stably transfected cells, resulted in impaired signaling via the wildtype GNRHR by reducing maximal agonist-induced inositol phosphate accumulation. This inhibitory effect depended on the amount of splice variant cDNA cotransfected and was specific for GNRHR. Coexpression of the wildtype and truncated GNRHRs resulted in impaired insertion of wildtype GNRHR into the plasma membrane. Caron et al. (1999) studied a kindred with 3 sibs with isolated hypogonadotropic hypogonadism who were genetic compounds for the arg262-to-gln mutation (138850.0002) and an ala129-to-aspartate (138850.0004) mutation that resulted in a complete loss of function. The 2 brothers had micropallus and bilateral cryptorchidism and were referred for lack of puberty; their sister had primary amenorrhea and a complete lack of puberty. The authors concluded that these hypogonadal patients were partially resistant to pulsatile GNRH administration, suggesting that they should be treated with gonadotropins to

induce spermatogenesis or ovulation rather than with pulsatile GnRH. Kottler et al. (1999) analyzed in detail the GnRHR mutations in 7 independent familial and sporadic cases of idiopathic hypogonadotropic hypogonadism reported to that time. The Q106R (138850.0001) and R262Q (138850.0002) mutations were frequent in patients from all geographic areas (North or South America or Europe).

[0578] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0579] Caron, P.; Chauvin, S.; Christin-Maitre, S.; Bennet, A.; Lahlou, N.; Counis, R.; Bouchard, P.; Kottler, M.-L. : Resistance of hypogonadic patients with mutated GnRH receptor genes to pulsatile GnRH administration. J. Clin. Endocr. Metab. 84: 990-996, 1999. ; and

[0580] Kakar, S. S.; Musgrove, L. C.; Devor, D. C.; Sellers, J. C.; Neill, J. D. : Cloning, sequencing, and expression of human gonadotropin releasing hormone (GnRH) receptor. Biochem. Biophys.

[0581] Further studies establishing the function and utilities of GnRHR are found in John Hopkins OMIM database record ID 138850, and in cited publications numbered 167-17

and 174–188 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. HIS1 (Accession NM_006460) is another VGAM23 host target gene. HIS1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by HIS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HIS1 BINDING SITE, designated SEQ ID:105, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0582] Another function of VGAM23 is therefore inhibition of HIS1 (Accession NM_006460). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HIS1. Heterogeneous Nuclear Ribonucleoprotein D-like (HNRPDL, Accession NM_005463) is another VGAM23 host target gene. HNRPDL BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HNRPDL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HNRPDL BINDING SITE, designated SEQ

ID:92, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0583] Another function of VGAM23 is therefore inhibition of Heterogeneous Nuclear Ribonucleoprotein D-like (HNRPDL, Accession NM_005463), a gene which binds to rna molecules that contain au-rich elements. Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HNRPDL. The function of HNRPDL has been established by previous studies. Kamei et al. (1999) identified 2 isoforms of HNRPDL, which they called JKTBP1 and JKTBP2, corresponding to the 1.4- and 2.8-kb transcripts identified by Tsuchiya et al. (1998), respectively. The larger transcript predicts a 420-amino acid protein with a calculated molecular mass of approximately 46.4 kD. The JKTBP2 protein has a longer N terminus, and both proteins contain multiple potential sites for phosphorylation and arginine methylation. Northern blot analysis showed that both transcripts were expressed in all tissues examined, although the amounts and ratios of the transcripts varied in different tissues. Three JKTBP transcripts greater than 2.8 kb were expressed in pancreas, spleen, and thymus. Western blot analysis of myeloid leukemia cells showed

proteins of 38 and 53 kD. Tsuchiya et al. (1998) determined that recombinant HNRPDL interacted with both the double- and single-stranded forms of JKT41, an oligodeoxynucleotide corresponding to the cis-acting element in intron 9 of the MPO gene. Recombinant HNRPDL also interacted with poly(G) and poly(A), but not with poly(U) or poly(C). Transient expression of HNRPDL repressed expression of reporter genes located downstream of the intron 9 element of JKT41 or the intron 7 element of FERE27, another oligodeoxynucleotide corresponding to MPO.

[0584] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0585] Kamei, D.; Tsuchiya, N.; Yamazaki, M.; Meguro, H.; Yamada, M. : Two forms of expression and genomic structure of the human heterogeneous nuclear ribonucleoprotein D-like JKTBP gene (HNRPDL). *Gene* 228: 13-22, 1999.
; and

[0586] Tsuchiya, N.; Kamei, D.; Takano, A.; Matsui, T.; Yamada, M. : Cloning and characterization of a cDNA encoding a novel heterogeneous nuclear ribonucleoprotein-like protein and its expressio.

[0587] Further studies establishing the function and utilities of HNRPDL are found in John Hopkins OMIM database record ID 607137, and in cited publications numbered 271–273 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Inhibin, Beta A (activin A, activin AB alpha polypeptide) (INHBA, Accession NM_002192) is another VGAM23 host target gene. INHBA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by INHBA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of INHBA BINDING SITE, designated SEQ ID:59, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0588] Another function of VGAM23 is therefore inhibition of Inhibin, Beta A (activin A, activin AB alpha polypeptide) (INHBA, Accession NM_002192), a gene which inhibits respectively the secretion of follitropin by the pituitary gland. Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with INHBA. The function of INHBA has been established by previous studies. From the culture

fluid of a human transformed cell line (THB-1) stimulated by phorbol 12-myristate 13-acetate, Murata et al. (1988) isolated a protein that exhibited potent differentiation-inducing activity toward mouse Friend erythroleukemia cells and human K-562 cells. Designated erythroid differentiation factor (EDF), the protein is a homodimer with a molecular weight of 25,000. Surprisingly, the sequence of EDF mRNA was found to be identical to that of the beta-A subunit of inhibin. Southern blot analysis indicated that only 1 gene for EDF/inhibin beta-A exists in the human genome. The follicle-stimulating hormone (FSH)-releasing protein (FRP) subunit is likewise identical in structure to the beta-A subunit of inhibin. Lumpkin et al. (1987) purified from sheep hypothalamus a fraction (presumably a peptide) that had selective FSH-releasing properties. They demonstrated dissimilarity of the purified factor from luteinizing hormone-releasing hormone (OMIM Ref. No. 152760). You and Kruse (2002) studied corneal myofibroblast differentiation and signal transduction induced by the transforming growth factor-beta (TGFB) family members activin A and bone morphogenetic protein-7 (BMP7; 112267). They found that activin A induced phosphorylation of SMAD2 (OMIM Ref. No. 601366), and BMP7

induced SMAD1 (OMIM Ref. No. 601595), both of which were inhibited by follistatin (OMIM Ref. No. 136470). Transfection with antisense SMAD2/SMAD3 (OMIM Ref. No. 603109) prevented activin-induced expression and accumulation of alpha-smooth muscle actin. The authors concluded that TGFB proteins have different functions in the cornea. Activin A and TGFB1, but not BMP7, are regulators of keratocyte differentiation and might play a role during myofibroblast transdifferentiation. SMAD2/SMAD3 signal transduction appeared to be important in the regulation of muscle-specific genes. Animal model experiments lend further support to the function of INHBA. The activins, dimers of beta-A or beta-B subunits encoded by the genes *Inhba* and *Inhbb*, respectively, are TGF-beta superfamily members that have roles in reproduction and development. Whereas mice homozygous for the *Inhba*-null allele demonstrate disruption of whisker, palate, and tooth development leading to neonatal lethality, homozygous *Inhbb*-null mice are viable, fertile, and have eye defects. To determine if these phenotypes were due to spatiotemporal expression differences of the ligands or disruption of specific ligand-receptor interactions, Brown et al. (2000) replaced the region of *Inhba* encoding the ma-

ture protein with Inhbb, creating the allele designated Inhba(BK). Although the craniofacial phenotypes of the Inhba-null mutation were rescued by the Inhba(BK) allele, somatic, testicular, genital, and hair growth were grossly affected and influenced by the dosage and bioactivity of the allele. Thus, Brown et al. (2000) concluded that functional compensation within the TGF-beta superfamily can occur if the replacement gene is expressed appropriately. The novel phenotypes in these mice further illustrate the usefulness of insertion strategies for defining protein function. The structural organization of the testes of adult Inhba(BK/BK) mice was normal; however, the differentiation of the seminiferous tubules of Inhba(BK/-) mice was delayed. The testicular volumes of both Inhba(BK/BK) and Inhba(BK/-) mice were less than those of controls, and the dosage of the Inhba(BK) allele correlated positively with testicular size. Inhba(+ /BK) males had normal onset of fertility, whereas Inhba(BK/BK) males had delayed onset of fertility similar to Acvr2 (OMIM Ref. No. 102581) -/- mice. Only 1 in 6 Inhba(BK/BK) females produced litters, whereas Inhba(+ /BK) females were normally fertile. The ovaries of Inhba(BK/-) mice were smaller and contained fewer large preantral follicles than those of controls. In-

hba(BK/BK) and Inhba(BK/–) mice were identified by their smaller size, slower hair growth, the rough appearance of their fur, and sunken eyes. Approximately 50% of Inhba(BK/BK) mice died by 26 weeks, whereas Inhba(BK/–) mice invariably became cachectic and died between 3 and 4 weeks. The summary of phenotypic findings of Inhba(BK/–) mice includes short whiskers, normal tooth development, no cleft palate, symmetric growth deficiency (OMIM Ref. No. severe), enlargement of external genitalia, hypogonadism (OMIM Ref. No. severe), delayed hair growth (moderate), hypoglycemia (mild), decreased life expectancy (OMIM Ref. No. severe), and anemia

[0589] It is appreciated that the abovementioned animal model for INHBA is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[0590] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0591] Brown, C. W.; Houston-Hawkins, D. E.; Woodruff, T. K.; Matzuk, M. M. : Insertion of Inhbb into the Inhba locus rescues the Inhba-null phenotype and reveals new activin functions. Nature Genet. 25: 453–457, 2000. ; and

[0592] Murata, M.; Eto, Y.; Shibai, H.; Sakai, M.; Muramatsu, M. : Erythroid differentiation factor is encoded by the same mRNA as that of the inhibin beta-A chain. Proc. Nat. Acad. Sci. 85: 2.

[0593] Further studies establishing the function and utilities of INHBA are found in John Hopkins OMIM database record ID 147290, and in cited publications numbered 235, 23 and 238–242 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Kinesin Family Member 3B (KIF3B, Accession NM_004798) is another VGAM23 host target gene. KIF3B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIF3B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIF3B BINDING SITE, designated SEQ ID:87, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0594] Another function of VGAM23 is therefore inhibition of Kinesin Family Member 3B (KIF3B, Accession NM_004798), a gene which is a microtubule-based anterograde translocator for membranous organelles. Accordingly, utilities of

VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIF3B. The function of KIF3B has been established by previous studies. In eukaryotic cells, proteins and lipids are sorted and transported to their correct destinations at distinct velocities by each organelle or protein complex. Kinesin superfamily proteins are a molecular motor superfamily involved in these processes, conveying their own cargoes along microtubules. Nagase et al. (1997) cloned the KIF3B gene, which they referred to as KIAA0359, the human homolog of the mouse kinase superfamily 3B gene (Yamazaki et al., 1995). The human KIF3B gene encodes a 747-amino acid protein that shares 98% identity with the mouse Kif3b protein. RT-PCR analysis revealed that the KIF3B gene was ubiquitously expressed in all human tissues tested. By analysis of radiation hybrid panels, Nagase et al. (1997) mapped the KIF3B gene to chromosome 20. Animal model experiments lend further support to the function of KIF3B. By gene targeting, Nonaka et al. (1998) disrupted the murine Kif3b gene. The null mutants did not survive beyond midgestation, exhibiting growth retardation, pericardial sac ballooning, and neural tube disorganization. Prominently, the left-right asymmetry was ran-

domized in the heart loop and the direction of embryonic turning. Lefty-2 (OMIM Ref. No. 603037) expression was either bilateral or absent. Furthermore, the node lacked monocilia while the basal bodies were present. Immunocytochemistry revealed Kif3b localization in wildtype nodal cilia. Video microscopy showed that these cilia were motile and generated a leftward flow. These data suggested that KIF3B is essential for the left-right determination through intraciliary transportation of materials for ciliogenesis of motile primary cilia that could produce a gradient of putative morphogen along the left-right axis in the node

[0595] It is appreciated that the abovementioned animal model for KIF3B is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[0596] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0597] Nagase, T.; Ishikawa, K.; Nakajima, D.; Ohira, M.; Seki, N.; Miyajima, N.; Tanaka, A.; Kotani, H.; Nomura, N.; Ohara, O. : Prediction of the coding sequences of unidentified human genes. VII. The complete sequences of 100 new

cDNA clones from brain which can code for large proteins in vitro. DNA Res. 4: 141–150, 1997. ; and

[0598] Nonaka, S.; Tanaka, Y.; Okada, Y.; Takeda, S.; Harada, A.; Kanai, Y.; Kido, M.; Hirokawa, N. : Randomization of left–right asymmetry due to loss of nodal cilia generating left–ward flow.

[0599] Further studies establishing the function and utilities of KIF3B are found in John Hopkins OMIM database record ID 603754, and in cited publications numbered 3 and 395–396 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Moesin (MSN, Accession XM_013042) is another VGAM23 host target gene. MSN BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by MSN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MSN BINDING SITE, designated SEQ ID:262, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0600] Another function of VGAM23 is therefore inhibition of Moesin (MSN, Accession XM_013042), a gene which may have a role linking the cytoskeleton to the plasma mem–

brane. Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MSN. The function of MSN has been established by previous studies. Shcherbina et al. (1999) demonstrated a decrease in platelet moesin in patients with Wiskott–Aldrich syndrome (OMIM Ref. No. 301000). This appeared to be a secondary defect to the primary defect in the WASP gene. The WASP and MSN genes are both located on the X chromosome, on the short and the long arm, respectively. Using mouse helper T cell lines and confocal microscopy, Allenspach et al. (2001) determined that the cytoplasmic tail of CD43 is necessary and sufficient for CD43 removal from the immunologic synapse. In at least some cells, CD43 is located at the distal pole of the T cell together with ezrin and moesin. No differences in the behavior of ezrin and moesin were noted throughout the study. Using cells from Cd43 $-/-$ mice, Allenspach et al. (2001) observed that ezrin–radixin–moesin (ERM) family proteins move independently of the large CD43 mucin. Overexpression of a dominant–negative ERM mutant containing the N–terminal 320 amino acids of ezrin inhibited the activation–induced movement of CD43 without affecting conjugate formation. The dominant–negative

mutant reduced cytokine production but not the expression of T-cell activation markers.

[0601] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0602] Lankes, W.; Griesmacher, A.; Grunwald, J.; Schwartz-Albiez, R.; Keller, R. : A heparin-binding protein involved in inhibition of smooth-muscle cell proliferation. *Biochem. J.* 251: 831-842, 1988. ; and

[0603] Lankes, W. T.; Furthmayr, H. : Moesin: a member of the protein 4.1-talin-ezrin family of proteins. *Proc. Nat. Acad. Sci.* 88: 8297-8301, 1991.

[0604] Further studies establishing the function and utilities of MSN are found in John Hopkins OMIM database record ID 309845, and in cited publications numbered 19 and 469-472 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. 5-methyltetrahydrofolate-homocysteine Methyltransferase (MTR, Accession NM_000254) is another VGAM23 host target gene. MTR BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MTR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MTR BINDING SITE, designated SEQ ID:36, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0605] Another function of VGAM23 is therefore inhibition of 5-methyltetrahydrofolate-homocysteine Methyltransferase (MTR, Accession NM_000254). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MTR. Protocadherin Beta 9 (PCDHB9, Accession NM_019119) is another VGAM23 host target gene. PCDHB9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PCDHB9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDHB9 BINDING SITE, designated SEQ ID:169, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0606] Another function of VGAM23 is therefore inhibition of Protocadherin Beta 9 (PCDHB9, Accession NM_019119), a gene which is a potential calcium-dependent cell-

adhesion protein. Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDHB9. The function of PCDHB9 has been established by previous studies. Cadherins are calcium-dependent cell-cell adhesion molecules that mediate neural cell-cell interactions. Protocadherins constitute a subfamily of nonclassic cadherins. PCDHB9 is a member of the beta cluster of protocadherin genes on 5q31. For specific information on the PCDHB genes, see 604967. Vanhalst et al. (2001) determined that unlike most PCDHB proteins, PCDHB9 has not 1 but 2 PXXP motifs, putative SH3 protein-binding sites, at the end of the conserved region of its cytoplasmic domain.

[0607] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0608] Vanhalst, K.; Kools, P.; Eynde, E. V.; van Roy, F. : The human and murine protocadherin-beta one-exon gene families show high evolutionary conservation, despite the difference in gene number. FEBS Lett. 495: 120-125, 2001. ; and

[0609] Wu, Q.; Zhang, T.; Cheng, J.-F.; Kim, Y.; Grimwood, J.;

Schmutz, J.; Dickson, M.; Noonan, J. P.; Zhang, M. Q.; Myers, R. M.; Maniatis, T. : Comparative DNA sequence analysis of mouse a.

[0610] Further studies establishing the function and utilities of PCDHB9 are found in John Hopkins OMIM database record ID 606335, and in cited publications numbered 30 and 481 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily A, Member 3 (SMARCA3, Accession NM_139048) is another VGAM23 host target gene.

SMARCA3 BINDING SITE1 and SMARCA3 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by SMARCA3, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SMARCA3 BINDING SITE1 and SMARCA3 BINDING SITE2, designated SEQ ID:246 and SEQ ID:66 respectively, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0611] Another function of VGAM23 is therefore inhibition of SWI/SNF Related, Matrix Associated, Actin Dependent

Regulator of Chromatin, Subfamily A, Member 3

(SMARCA3, Accession NM_139048), a gene which is involved in chromatin assembly and remodeling. Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SMARCA3. The function of SMARCA3 has been established by previous studies. Chromatin remodeling enzymes are implicated in a variety of important cellular functions. Various components of chromatin remodeling complexes, including several members of the SWI/SNF family, are disrupted in cancer. Moinova et al. (2002) identified the HLTF gene (SMARCA3) as a target for gene inactivation in colon cancer. Loss of HLTF expression accompanied by HLTF promoter methylation was noted in 9 of 34 colon cancer cell lines. In these cell lines, HLTF expression was restored by treatment with the demethylating agent 5-azacytidine. In further studies of primary colon cancer tissues, HLTF methylation was detected in 27 of 63 cases (43%). No methylation of HLTF was detected in breast or lung cancers, suggesting selection for HLTF methylation in colonic malignancies. Transfection of HLTF suppressed 75% of colon growth in each of 3 different HLTF-deficient cell lines, but showed no suppressive ef-

fect in any of 3 HLTF-proficient cell lines. These findings showed that HLTF is a common target for methylation and epigenetic gene silencing in colon cancer and suggested HLTF as a candidate colon cancer suppressor gene.

[0612] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0613] Moinova, H. R.; Chen, W.-D.; Shen, L.; Smiraglia, D.; Olechnowicz, J.; Ravi, L.; Kasturi, L.; Myeroff, L.; Plass, C.; Parsons, R.; Minna, J.; Willson, J. K. V.; Green, S. B.; Issa, J.-P.; Markowitz, S. D. : HLTF gene silencing in human colon cancer. Proc. Nat. Acad. Sci. 99: 4562-4567, 2002. ; and

[0614] Sheridan, P. L.; Schorpp, Ding, H.; Descheemaeker, K.; Marynen, P.; Nelles, L.; Carvalho, T.; Carmo-Fonseca, M.; Collen, D.; Belayew, A. : Characterization of a helicase-like transcrip.

[0615] Further studies establishing the function and utilities of SMARCA3 are found in John Hopkins OMIM database record ID 603257, and in cited publications numbered 454-457 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Synuclein, Alpha Interacting Protein (synphilin)

(SNCAIP, Accession XM_171090) is another VGAM23 host target gene. SNCAIP BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SNCAIP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SNCAIP BINDING SITE, designated SEQ ID:399, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0616] Another function of VGAM23 is therefore inhibition of Synuclein, Alpha Interacting Protein (synphilin) (SNCAIP, Accession XM_171090), a gene which promotes formation of cytosolic inclusions in neurons. Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SNCAIP. The function of SNCAIP has been established by previous studies. Parkinson disease (PD) is a neurodegenerative disease characterized by tremor, bradykinesia, rigidity, and postural instability. Postmortem examination shows loss of neurons and Lewy bodies, which are cytoplasmic eosinophilic inclusions, in the substantia nigra and other brain regions. A few families have been found to have PD on the basis of mutations, A53T (163890.0001) or A30P

(163890.0002), in the gene encoding alpha-synuclein (SNCA). Alpha-synuclein is present in Lewy bodies of patients with sporadic PD, suggesting that alpha-synuclein may be involved in the pathogenesis of PD. To determine the protein-interaction partners of alpha-synuclein, Engender et al. (1999) screened human brain libraries in the yeast 2-hybrid system. They identified a novel interacting protein they designated synphilin-1, encoded by the gene SNCAIP. The predicted 919-amino acid synphilin-1 protein contains several protein-protein interaction domains, such as ankyrin-like repeats and a coiled-coil domain. An approximately 4-kb SNCAIP transcript was detected in many human tissues by Northern blot analysis and was particularly enriched in brain, heart, and placenta. Synphilin-1 was present in many regions in brain, including substantia nigra. In immunoblot analyses of human brain, synphilin-1 appeared as a single band of approximately 90 kD in several brain regions, with no differences in the level of expression in controls, patients with PD, or patients with Alzheimer disease (OMIM Ref. No. 104300). They found that alpha-synuclein interacts in vivo with synphilin-1 in neurons. Cotransfection of both proteins (but not control proteins) in HEK293 cells yielded cyto-

plasmic eosinophilic inclusions. Engelender et al. (2000) determined that the human SNCAIP gene contains 10 exons and has a highly polymorphic GT repeat within intron 5 that is suitable for linkage analysis in families with Parkinson disease. Using immunohistochemistry in human postmortem brain tissue, they found that synphilin-1 protein, like alpha-synuclein protein, is present in neuropil.

[0617] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0618] Engelender, S.; Kaminsky, Z.; Guo, X.; Sharp, A. H.; Amaravi, R. K.; Kleiderlein, J. J.; Margolis, R. L.; Troncoso, J. C.; Lanahan, A. A.; Worley, P. F.; Dawson, V. L.; Dawson, T. M.; Ross, C. A. : Synphilin-1 associates with alpha-synuclein and promotes the formation of cytosolic inclusions. *Nature Genet.* 22: 110-114, 1999. ; and

[0619] Engelender, S.; Wanner, T.; Kleiderlein, J. J.; Wakabayashi, K.; Tsuji, S.; Takahashi, H.; Ashworth, R.; Margolis, R. L.; Ross, C. A. : Organization of the human synphilin-1 gene, a ca.

[0620] Further studies establishing the function and utilities of SNCAIP are found in John Hopkins OMIM database record ID 603779, and in cited publications numbered 6 and 438

listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Synaptogyrin 1 (SYNGR1, Accession NM_004711) is another VGAM23 host target gene. SYNGR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SYNGR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SYNGR1 BINDING SITE, designated SEQ ID:86, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0621] Another function of VGAM23 is therefore inhibition of Synaptogyrin 1 (SYNGR1, Accession NM_004711), a gene which belongs to transmembrane synaptic vesicle protein and may function in membrane recycling. Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SYNGR1. The function of SYNGR1 has been established by previous studies. Rat synaptogyrin, or RAT-SYNGR1, is an integral membrane protein associated with presynaptic vesicles in neuronal cells. See SYNGR2 (OMIM Ref. No. 603926). As part of an effort to sequence the

long arm of human chromosome 22, Kedra et al. (1998) identified the human homolog of RATSYNGR1, synaptogyrin-1 (OMIM Ref. No. SYNGR1). By a combination of EST database searching and library screening, the authors isolated cDNAs corresponding to 3 alternatively spliced transcripts, which they designated SYNGR1a-c. The predicted 1a, 1b, and 1c proteins contain 234, 191, and 192 amino acids, respectively. Northern blot analysis revealed that the 4.5-kb SYNGR1a mRNA is expressed at high levels in brain. The other transcript forms are expressed at low levels in nonneuronal tissues. In situ hybridization to embryonic and adult mouse tissues confirmed that SYNGR1a, the most abundant transcript form, shows predominantly neuronal expression. Kedra et al. (1998) also identified cDNAs encoding the related human proteins SYNGR2 and SYNGR3 (OMIM Ref. No. 603927) and mouse Syngr1b. Like RATSYNGR1, the mouse and human synaptogyrin family members contain 4 membrane-spanning domains. The conserved central portion of SYNGR1a shares 54%, 61%, and 92% identity with that of SYNGR2, SYNGR3, and RATSYNGR1, respectively. Animal model experiments lend further support to the function of SYNGR1. Using gene targeting, Janz et al. (1999) generated mice lacking

Syngr1. They bred these Syngr1 knockout mice against Syp (OMIM Ref. No. 313475) knockout mice generated by McMahon et al. (1996) to create double knockout mice deficient in both Syp and Syngr1. Both single and double knockout mice were viable and fertile. Morphologic and biochemical analysis showed that the architecture and composition of synapses were unaltered in the brains of Syngr1 single knockout and Syngr1/Syp double knockout mutant mice. Electrophysiologic recordings in the hippocampal CA1 region revealed that short- and long-term synaptic plasticity was severely reduced in the Syngr1/Syp double knockout mice without changes in the fundamental release apparatus, vesicle cycling, or release probability. Janz et al. (1999) concluded that Syngr1 and Syp perform essential and redundant functions in synaptic plasticity without being required for synaptic transmission as such.

[0622] It is appreciated that the abovementioned animal model for SYNGR1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[0623] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [0624] Janz, R.; Sudhof, T. C.; Hammer, R. E.; Unni, V.; Siegelbaum, S. A.; Bolshakov, V. Y. : Essential roles in synaptic plasticity for synaptogyrin I and synaptophysin I. *Neuron* 24: 687–700, 1999. ; and
- [0625] Kedra, D.; Pan, H.–Q.; Seroussi, E.; Fransson, I.; Guilbaud, C.; Collins, J. E.; Dunham, I.; Blennow, E.; Roe, B. A.; Piehl, F.; Dumanski, J. P. : Characterization of the human synapto.
- [0626] Further studies establishing the function and utilities of SYNGR1 are found in John Hopkins OMIM database record ID 603925, and in cited publications numbered 43 and 437 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Uncoupling Protein 2 (mitochondrial, proton carrier) (UCP2, Accession NM_003355) is another VGAM23 host target gene. UCP2 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by UCP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UCP2 BINDING SITE, designated SEQ ID:68, to the nucleotide sequence of VGAM23 RNA, herein designated

VGAM RNA, also designated SEQ ID:24.

[0627] Another function of VGAM23 is therefore inhibition of Uncoupling Protein 2 (mitochondrial, proton carrier) (UCP2, Accession NM_003355), a gene which is an inner mitochondrial membrane transporter and uncouples electron transport from oxidative phosphorylation. Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UCP2. The function of UCP2 has been established by previous studies. Esterbauer et al. (2001) showed that a common G/A polymorphism in the UCP2 promoter region is associated with enhanced adipose tissue mRNA expression in vivo and results in increased transcription of a reporter gene in the human adipocyte cell line PAZ-6. In analyzing 340 obese and 256 never-obese middle-aged subjects, they found a modest but significant reduction in obesity prevalence associated with the less-common allele. They confirmed this association in a population-based sample of 791 middle-aged subjects from the same geographic area (Salzburg, Austria). Despite its modest effect, but because of its high frequency (approximately 63%), the more-common risk allele conferred a relatively large population-attributable risk accounting for 15% of

the obesity in the population studied. Animal model experiments lend further support to the function of UCP2. Zhang et al. (2001) assessed the role of UCP2 in regulating insulin secretion. Ucp2-deficient mice had higher islet ATP levels and increased glucose-stimulated insulin secretion, establishing that UCP2 negatively regulates insulin secretion. Of pathophysiologic significance, Ucp2 was markedly upregulated in islets of ob/ob mice, a model of obesity-induced diabetes. Ob/ob mice lacking Ucp2 had restored first-phase insulin secretion, increased serum insulin levels, and greatly decreased levels of glycemia. These results established UCP2 as a key component of beta-cell glucose sensing and as a critical link between obesity, beta-cell dysfunction, and type II diabetes.

[0628] It is appreciated that the abovementioned animal model for UCP2 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[0629] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0630] Esterbauer, H.; Schneitler, C.; Oberkofler, H.; Ebenbichler, C.; Paulweber, B.; Sandhofer, F.; Ladurner, G.; Hell, E.;

Strosberg, A. D.; Patsch, J. R.; Krempler, F.; Patsch, W. : A common polymorphism in the promoter of UCP2 is associated with decreased risk of obesity in middle-aged humans. *Nature Genet.* 28: 178–183, 2001. ; and

[0631] Zhang, C.-Y.; Baffy, G.; Perret, P.; Krauss, S.; Peroni, O.; Grujic, D.; Hagen, T.; Vidal-Puig, A.; Boss, O.; Kim, Y.-B.; Zheng, X. X.; Wheeler, M. B.; Shulman, G. I.; Chan, C. B.; Lo.

[0632] Further studies establishing the function and utilities of UCP2 are found in John Hopkins OMIM database record ID 601693, and in cited publications numbered 280–282, 163–164, 283–286, 8 and 293 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. BMF (Accession NM_033503) is another VGAM23 host target gene. BMF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BMF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BMF BINDING SITE, designated SEQ ID:229, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0633] Another function of VGAM23 is therefore inhibition of BMF (Accession NM_033503). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BMF.

BCL2/adenovirus E1B 19kDa Interacting Protein 2 (BNIP2, Accession XM_039703) is another VGAM23 host target gene. BNIP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BNIP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BNIP2 BINDING SITE, designated SEQ ID:278, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0634] Another function of VGAM23 is therefore inhibition of BCL2/adenovirus E1B 19kDa Interacting Protein 2 (BNIP2, Accession XM_039703). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BNIP2. DEAD/H (Asp-Glu-Ala-Asp/His) Box Polypeptide 33 (DDX33, Accession NM_020162) is another VGAM23 host target gene. DDX33 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

DDX33, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DDX33 BINDING SITE, designated SEQ ID:171, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0635] Another function of VGAM23 is therefore inhibition of DEAD/H (Asp-Glu-Ala-Asp/His) Box Polypeptide 33 (DDX33, Accession NM_020162). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DDX33. Echinoderm Microtubule Associated Protein Like 4 (EML4, Accession NM_019063) is another VGAM23 host target gene. EML4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EML4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EML4 BINDING SITE, designated SEQ ID:168, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0636] Another function of VGAM23 is therefore inhibition of Echinoderm Microtubule Associated Protein Like 4 (EML4,

Accession NM_019063). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EML4. EPB41L4 (Accession NM_022140) is another VGAM23 host target gene. EPB41L4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EPB41L4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EPB41L4 BINDING SITE, designated SEQ ID:187, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0637] Another function of VGAM23 is therefore inhibition of EPB41L4 (Accession NM_022140). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EPB41L4. FLJ11588 (Accession NM_024603) is another VGAM23 host target gene. FLJ11588 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ11588, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11588 BINDING SITE,

designated SEQ ID:199, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0638] Another function of VGAM23 is therefore inhibition of FLJ11588 (Accession NM_024603). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11588. FLJ20150 (Accession NM_017688) is another VGAM23 host target gene. FLJ20150 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20150, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20150 BINDING SITE, designated SEQ ID:153, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0639] Another function of VGAM23 is therefore inhibition of FLJ20150 (Accession NM_017688). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20150. FLJ20507 (Accession NM_017849) is another VGAM23 host target gene. FLJ20507 BINDING SITE1 and FLJ20507

BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by FLJ20507, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20507 BINDING SITE1 and FLJ20507 BINDING SITE2, designated SEQ ID:154 and SEQ ID:261 respectively, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0640] Another function of VGAM23 is therefore inhibition of FLJ20507 (Accession NM_017849). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20507. FLJ22233 (Accession NM_024959) is another VGAM23 host target gene. FLJ22233 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ22233, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22233 BINDING SITE, designated SEQ ID:204, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0641] Another function of VGAM23 is therefore inhibition of FLJ22233 (Accession NM_024959). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22233. FLJ23191 (Accession NM_024574) is another VGAM23 host target gene. FLJ23191 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23191, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23191 BINDING SITE, designated SEQ ID:198, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0642] Another function of VGAM23 is therefore inhibition of FLJ23191 (Accession NM_024574). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23191. FLJ23468 (Accession NM_024629) is another VGAM23 host target gene. FLJ23468 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ23468, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23468 BINDING SITE, designated SEQ ID:200, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0643] Another function of VGAM23 is therefore inhibition of FLJ23468 (Accession NM_024629). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23468. G Protein-coupled Receptor Kinase-interactor 2 (GIT2, Accession NM_014776) is another VGAM23 host target gene. GIT2 BINDING SITE1 through GIT2 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by GIT2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GIT2 BINDING SITE1 through GIT2 BINDING SITE3, designated SEQ ID:133, SEQ ID:231 and SEQ ID:232 respectively, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0644] Another function of VGAM23 is therefore inhibition of G Protein-coupled Receptor Kinase-interactor 2 (GIT2, Ac-

cession NM_014776). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GIT2. GT650 (Accession NM_052851) is another VGAM23 host target gene. GT650 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GT650, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GT650 BINDING SITE, designated SEQ ID:230, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0645] Another function of VGAM23 is therefore inhibition of GT650 (Accession NM_052851). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GT650. IKKE (Accession NM_014002) is another VGAM23 host target gene. IKKE BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IKKE, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IKKE BINDING SITE, designated SEQ ID:124, to

the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0646] Another function of VGAM23 is therefore inhibition of IKKE (Accession NM_014002). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IKKE. KIAA0254 (Accession NM_014758) is another VGAM23 host target gene. KIAA0254 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0254, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0254 BINDING SITE, designated SEQ ID:131, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0647] Another function of VGAM23 is therefore inhibition of KIAA0254 (Accession NM_014758). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0254. KIAA1026 (Accession XM_048825) is another VGAM23 host target gene. KIAA1026 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by KIAA1026, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1026 BINDING SITE, designated SEQ ID:292, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0648] Another function of VGAM23 is therefore inhibition of KIAA1026 (Accession XM_048825). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1026. KIAA1163 (Accession XM_086231) is another VGAM23 host target gene. KIAA1163 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1163, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1163 BINDING SITE, designated SEQ ID:331, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0649] Another function of VGAM23 is therefore inhibition of KIAA1163 (Accession XM_086231). Accordingly, utilities

of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1163. KIAA1598 (Accession NM_018330) is another VGAM23 host target gene. KIAA1598 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1598, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1598 BINDING SITE, designated SEQ ID:161, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0650] Another function of VGAM23 is therefore inhibition of KIAA1598 (Accession NM_018330). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1598. KIAA1853 (Accession XM_045184) is another VGAM23 host target gene. KIAA1853 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1853, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

KIAA1853 BINDING SITE, designated SEQ ID:287, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0651] Another function of VGAM23 is therefore inhibition of KIAA1853 (Accession XM_045184). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1853. Lysyl Oxidase-like 4 (LOXL4, Accession NM_032211) is another VGAM23 host target gene. LOXL4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOXL4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOXL4 BINDING SITE, designated SEQ ID:213, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0652] Another function of VGAM23 is therefore inhibition of Lysyl Oxidase-like 4 (LOXL4, Accession NM_032211). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOXL4. Methionyl Aminopeptidase 1 (METAP1, Accession XM_052334) is another VGAM23 host

target gene. METAP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by METAP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of METAP1 BINDING SITE, designated SEQ ID:298, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0653] Another function of VGAM23 is therefore inhibition of Methionyl Aminopeptidase 1 (METAP1, Accession XM_052334). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with METAP1. MGC11034 (Accession NM_031453) is another VGAM23 host target gene. MGC11034 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC11034, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC11034 BINDING SITE, designated SEQ ID:211, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ

ID:24.

[0654] Another function of VGAM23 is therefore inhibition of MGC11034 (Accession NM_031453). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC11034. MGC14128 (Accession NM_032899) is another VGAM23 host target gene. MGC14128 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC14128, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC14128 BINDING SITE, designated SEQ ID:222, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0655] Another function of VGAM23 is therefore inhibition of MGC14128 (Accession NM_032899). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC14128. MGC16175 (Accession NM_032765) is another VGAM23 host target gene. MGC16175 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC16175, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC16175 BINDING SITE, designated SEQ ID:219, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0656] Another function of VGAM23 is therefore inhibition of MGC16175 (Accession NM_032765). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC16175. MGC2752 (Accession XM_085842) is another VGAM23 host target gene. MGC2752 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC2752, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC2752 BINDING SITE, designated SEQ ID:327, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0657] Another function of VGAM23 is therefore inhibition of MGC2752 (Accession XM_085842). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with MGC2752. MGC34923 (Accession NM_144717) is another VGAM23 host target gene. MGC34923 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by MGC34923, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC34923 BINDING SITE, designated SEQ ID:254, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0658] Another function of VGAM23 is therefore inhibition of MGC34923 (Accession NM_144717). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC34923. Nuclear Receptor Subfamily 1, Group I, Member 3 (NR1I3, Accession NM_005122) is another VGAM23 host target gene. NR1I3 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by NR1I3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NR1I3 BINDING SITE, des-

ignated SEQ ID:89, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0659] Another function of VGAM23 is therefore inhibition of Nuclear Receptor Subfamily 1, Group I, Member 3 (NR1I3, Accession NM_005122). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NR1I3. NYD-SP15 (Accession NM_030911) is another VGAM23 host target gene. NYD-SP15 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NYD-SP15, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NYD-SP15 BINDING SITE, designated SEQ ID:208, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0660] Another function of VGAM23 is therefore inhibition of NYD-SP15 (Accession NM_030911). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NYD-SP15. Oxysterol Binding Protein-like 8 (OSBPL8, Accession

NM_020841) is another VGAM23 host target gene. OSBPL8 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by OSBPL8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OSBPL8 BINDING SITE, designated SEQ ID:177, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0661] Another function of VGAM23 is therefore inhibition of Oxysterol Binding Protein-like 8 (OSBPL8, Accession NM_020841). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OSBPL8. Pleckstrin Homology Domain Containing, Family A (phosphoinositide binding specific) Member 4 (PLEKHA4, Accession NM_020904) is another VGAM23 host target gene. PLEKHA4 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by PLEKHA4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PLEKHA4 BINDING SITE, designated SEQ ID:178, to the nucleotide

sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0662] Another function of VGAM23 is therefore inhibition of Pleckstrin Homology Domain Containing, Family A (phosphoinositide binding specific) Member 4 (PLEKHA4, Accession NM_020904). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PLEKHA4. Protein Kinase, Lysine Deficient 2 (PRKWINK2, Accession XM_117531) is another VGAM23 host target gene. PRKWINK2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRKWINK2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRKWINK2 BINDING SITE, designated SEQ ID:372, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0663] Another function of VGAM23 is therefore inhibition of Protein Kinase, Lysine Deficient 2 (PRKWINK2, Accession XM_117531). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRKWINK2. Proteasome

(prosome, macropain) 26S Subunit, Non-ATPase, 4 (PSMD4, Accession NM_002810) is another VGAM23 host target gene. PSMD4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PSMD4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PSMD4 BINDING SITE, designated SEQ ID:63, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0664] Another function of VGAM23 is therefore inhibition of Proteasome (prosome, macropain) 26S Subunit, Non-ATPase, 4 (PSMD4, Accession NM_002810). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PSMD4. RIS1 (Accession XM_087461) is another VGAM23 host target gene. RIS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RIS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RIS1 BINDING SITE, designated SEQ ID:337, to the nucleotide sequence of VGAM23

RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0665] Another function of VGAM23 is therefore inhibition of RIS1 (Accession XM_087461). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RIS1. Ring Finger Protein 24 (RNF24, Accession NM_007219) is another VGAM23 host target gene. RNF24 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RNF24, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RNF24 BINDING SITE, designated SEQ ID:114, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0666] Another function of VGAM23 is therefore inhibition of Ring Finger Protein 24 (RNF24, Accession NM_007219). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RNF24. SNRPN Upstream Reading Frame (SNURF, Accession NM_005678) is another VGAM23 host target gene. SNURF BINDING SITE is HOST TARGET binding

site found in the 3' untranslated region of mRNA encoded by SNURF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SNURF BINDING SITE, designated SEQ ID:96, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0667] Another function of VGAM23 is therefore inhibition of SNRPN Upstream Reading Frame (SNURF, Accession NM_005678). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SNURF. Sulfotransferase Family 4A, Member 1 (SULT4A1, Accession XM_043609) is another VGAM23 host target gene. SULT4A1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SULT4A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SULT4A1 BINDING SITE, designated SEQ ID:284, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0668] Another function of VGAM23 is therefore inhibition of Sul-

fotransferase Family 4A, Member 1 (SULT4A1, Accession XM_043609). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SULT4A1. SV2B (Accession NM_014848) is another VGAM23 host target gene. SV2B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SV2B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SV2B BINDING SITE, designated SEQ ID:135, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0669] Another function of VGAM23 is therefore inhibition of SV2B (Accession NM_014848). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SV2B. SZF1 (Accession NM_016089) is another VGAM23 host target gene. SZF1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SZF1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of SZF1 BINDING SITE, designated SEQ ID:147, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0670] Another function of VGAM23 is therefore inhibition of SZF1 (Accession NM_016089). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SZF1. Toll-like Receptor 10 (TLR10, Accession NM_030956) is another VGAM23 host target gene. TLR10 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by TLR10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TLR10 BINDING SITE, designated SEQ ID:210, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0671] Another function of VGAM23 is therefore inhibition of Toll-like Receptor 10 (TLR10, Accession NM_030956). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TLR10. Zinc Finger Protein 185 (LIM domain) (ZNF185, Accession NM_007150) is another VGAM23 host

target gene. ZNF185 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF185, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF185 BINDING SITE, designated SEQ ID:111, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0672] Another function of VGAM23 is therefore inhibition of Zinc Finger Protein 185 (LIM domain) (ZNF185, Accession NM_007150). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF185. LOC113612 (Accession XM_054492) is another VGAM23 host target gene. LOC113612 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC113612, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC113612 BINDING SITE, designated SEQ ID:300, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ

ID:24.

[0673] Another function of VGAM23 is therefore inhibition of LOC113612 (Accession XM_054492). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC113612. LOC133539 (Accession XM_059658) is another VGAM23 host target gene. LOC133539 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC133539, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC133539 BINDING SITE, designated SEQ ID:312, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0674] Another function of VGAM23 is therefore inhibition of LOC133539 (Accession XM_059658). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC133539. LOC139221 (Accession XM_066558) is another VGAM23 host target gene. LOC139221 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC139221, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC139221 BINDING SITE, designated SEQ ID:313, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0675] Another function of VGAM23 is therefore inhibition of LOC139221 (Accession XM_066558). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC139221. LOC142941 (Accession XM_096363) is another VGAM23 host target gene. LOC142941 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC142941, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC142941 BINDING SITE, designated SEQ ID:345, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0676] Another function of VGAM23 is therefore inhibition of LOC142941 (Accession XM_096363). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC142941. LOC145717 (Accession XM_039771) is another VGAM23 host target gene. LOC145717 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC145717, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145717 BINDING SITE, designated SEQ ID:279, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0677] Another function of VGAM23 is therefore inhibition of LOC145717 (Accession XM_039771). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145717. LOC147229 (Accession XM_085742) is another VGAM23 host target gene. LOC147229 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC147229, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147229 BINDING SITE, designated SEQ ID:325, to

the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0678] Another function of VGAM23 is therefore inhibition of LOC147229 (Accession XM_085742). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147229. LOC147658 (Accession XM_085827) is another VGAM23 host target gene. LOC147658 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC147658, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147658 BINDING SITE, designated SEQ ID:326, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0679] Another function of VGAM23 is therefore inhibition of LOC147658 (Accession XM_085827). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147658. LOC147920 (Accession XM_085932) is another VGAM23 host target gene. LOC147920 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC147920, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147920 BINDING SITE, designated SEQ ID:328, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0680] Another function of VGAM23 is therefore inhibition of LOC147920 (Accession XM_085932). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147920. LOC148894 (Accession XM_097542) is another VGAM23 host target gene. LOC148894 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC148894, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148894 BINDING SITE, designated SEQ ID:347, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0681] Another function of VGAM23 is therefore inhibition of LOC148894 (Accession XM_097542). Accordingly, utilities

of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148894. LOC150606 (Accession XM_097928) is another VGAM23 host target gene. LOC150606 BINDING SITE1 and LOC150606 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by LOC150606, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150606 BINDING SITE1 and LOC150606 BINDING SITE2, designated SEQ ID:349 and SEQ ID:350 respectively, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0682] Another function of VGAM23 is therefore inhibition of LOC150606 (Accession XM_097928). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150606. LOC155382 (Accession XM_098713) is another VGAM23 host target gene. LOC155382 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC155382, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC155382 BINDING SITE, designated SEQ ID:356, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0683] Another function of VGAM23 is therefore inhibition of LOC155382 (Accession XM_098713). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC155382. LOC157621 (Accession XM_098800) is another VGAM23 host target gene. LOC157621 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC157621, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157621 BINDING SITE, designated SEQ ID:358, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0684] Another function of VGAM23 is therefore inhibition of LOC157621 (Accession XM_098800). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC157621. LOC161528 (Accession XM_090961) is another VGAM23 host target gene. LOC161528 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC161528, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC161528 BINDING SITE, designated SEQ ID:342, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0685] Another function of VGAM23 is therefore inhibition of LOC161528 (Accession XM_090961). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC161528. LOC197114 (Accession XM_116987) is another VGAM23 host target gene. LOC197114 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC197114, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC197114 BINDING SITE, designated SEQ ID:369, to the nucleotide sequence of VGAM23 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:24.

[0686] Another function of VGAM23 is therefore inhibition of LOC197114 (Accession XM_116987). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC197114. LOC199883 (Accession XM_117150) is another VGAM23 host target gene. LOC199883 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC199883, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC199883 BINDING SITE, designated SEQ ID:370, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0687] Another function of VGAM23 is therefore inhibition of LOC199883 (Accession XM_117150). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC199883. LOC200020 (Accession XM_117179) is another VGAM23 host target gene. LOC200020 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200020, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200020 BINDING SITE, designated SEQ ID:371, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0688] Another function of VGAM23 is therefore inhibition of LOC200020 (Accession XM_117179). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200020. LOC200226 (Accession XM_114158) is another VGAM23 host target gene. LOC200226 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200226, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200226 BINDING SITE, designated SEQ ID:365, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0689] Another function of VGAM23 is therefore inhibition of LOC200226 (Accession XM_114158). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC200226. LOC204820 (Accession XM_119323) is another VGAM23 host target gene. LOC204820 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC204820, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC204820 BINDING SITE, designated SEQ ID:373, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0690] Another function of VGAM23 is therefore inhibition of LOC204820 (Accession XM_119323). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC204820. LOC219392 (Accession XM_165921) is another VGAM23 host target gene. LOC219392 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC219392, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219392 BINDING SITE, designated SEQ ID:377, to

the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0691] Another function of VGAM23 is therefore inhibition of LOC219392 (Accession XM_165921). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219392. LOC219800 (Accession XM_167774) is another VGAM23 host target gene. LOC219800 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219800, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219800 BINDING SITE, designated SEQ ID:389, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0692] Another function of VGAM23 is therefore inhibition of LOC219800 (Accession XM_167774). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219800. LOC220753 (Accession XM_167549) is another VGAM23 host target gene. LOC220753 BINDING SITE is HOST TARGET binding site found in the 5' un-

translated region of mRNA encoded by LOC220753, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220753 BINDING SITE, designated SEQ ID:388, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0693] Another function of VGAM23 is therefore inhibition of LOC220753 (Accession XM_167549). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220753. LOC220776 (Accession XM_043388) is another VGAM23 host target gene. LOC220776 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC220776, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220776 BINDING SITE, designated SEQ ID:283, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0694] Another function of VGAM23 is therefore inhibition of LOC220776 (Accession XM_043388). Accordingly, utilities

of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220776. LOC221454 (Accession XM_166448) is another VGAM23 host target gene. LOC221454 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC221454, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221454 BINDING SITE, designated SEQ ID:382, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0695] Another function of VGAM23 is therefore inhibition of LOC221454 (Accession XM_166448). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221454. LOC222444 (Accession XM_169425) is another VGAM23 host target gene. LOC222444 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC222444, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC222444 BINDING SITE, designated SEQ ID:392, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0696] Another function of VGAM23 is therefore inhibition of LOC222444 (Accession XM_169425). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC222444. LOC222962 (Accession XM_167291) is another VGAM23 host target gene. LOC222962 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC222962, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC222962 BINDING SITE, designated SEQ ID:387, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0697] Another function of VGAM23 is therefore inhibition of LOC222962 (Accession XM_167291). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC222962. LOC245727 (Accession XM_165913) is another VGAM23 host target gene. LOC245727 BINDING

SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC245727, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC245727 BINDING SITE, designated SEQ ID:376, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0698] Another function of VGAM23 is therefore inhibition of LOC245727 (Accession XM_165913). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC245727. LOC253525 (Accession XM_171868) is another VGAM23 host target gene. LOC253525 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC253525, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253525 BINDING SITE, designated SEQ ID:401, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0699] Another function of VGAM23 is therefore inhibition of

LOC253525 (Accession XM_171868). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253525. LOC254249 (Accession XM_170931) is another VGAM23 host target gene. LOC254249 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC254249, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254249 BINDING SITE, designated SEQ ID:397, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0700] Another function of VGAM23 is therefore inhibition of LOC254249 (Accession XM_170931). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254249. LOC255475 (Accession XM_174861) is another VGAM23 host target gene. LOC255475 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC255475, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC255475 BINDING SITE, designated SEQ ID:403, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0701] Another function of VGAM23 is therefore inhibition of LOC255475 (Accession XM_174861). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255475. LOC51026 (Accession NM_016072) is another VGAM23 host target gene. LOC51026 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51026, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51026 BINDING SITE, designated SEQ ID:146, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0702] Another function of VGAM23 is therefore inhibition of LOC51026 (Accession NM_016072). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51026. LOC91308 (Accession XM_037600) is another

VGAM23 host target gene. LOC91308 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91308, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91308 BINDING SITE, designated SEQ ID:274, to the nucleotide sequence of VGAM23 RNA, herein designated VGAM RNA, also designated SEQ ID:24.

[0703] Another function of VGAM23 is therefore inhibition of LOC91308 (Accession XM_037600). Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91308. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 24 (VGAM24) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0704] VGAM24 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM24 was detected is described

hereinabove with reference to Figs. 1–8.

[0705] VGAM24 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Immunodeficiency Virus 1. VGAM24 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0706] VGAM24 gene encodes a VGAM24 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM24 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM24 precursor RNA is designated SEQ ID:10, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:10 is located at position 1301 relative to the genome of Human Immunodeficiency Virus 1.

[0707] VGAM24 precursor RNA folds onto itself, forming VGAM24 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate

or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0708] An enzyme complex designated DICER COMPLEX, `dices` the VGAM24 folded precursor RNA into VGAM24 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 87%) nucleotide sequence of VGAM24 RNA is designated SEQ ID:25, and is provided hereinbelow with reference to the sequence listing part.

[0709] VGAM24 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM24 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM24 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[0710] VGAM24 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM24 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM24 RNA is an accurate or a partial inverted-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM24 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM24 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[0711] The complementary binding of VGAM24 RNA, herein designated VGAM RNA, to host target binding sites on VGAM24 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and

BINDING SITE III, inhibits translation of VGAM24 host target RNA into VGAM24 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0712] It is appreciated that VGAM24 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM24 host target genes. The mRNA of each one of this plurality of VGAM24 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM24 RNA, herein designated VGAM RNA, and which when bound by VGAM24 RNA causes inhibition of translation of respective one or more VGAM24 host target proteins.

[0713] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM24 gene, herein designated VGAM GENE, on one or more VGAM24 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only

for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[0714] It is yet further appreciated that a function of VGAM24 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM24 include diagnosis, prevention and treatment of viral infection by Human Immunodeficiency Virus 1. Specific functions, and accordingly utilities, of VGAM24 correlate with, and may be deduced from, the identity of the host target genes which VGAM24 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0715] Nucleotide sequences of the VGAM24 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM24 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM24 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM24 are further de-

scribed hereinbelow with reference to Table 1.

[0716] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM24 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM24 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0717] As mentioned hereinabove with reference to Fig. 1, a function of VGAM24 gene, herein designated VGAM is inhibition of expression of VGAM24 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM24 correlate with, and may be deduced from, the identity of the target genes which VGAM24 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[0718] Caspase 10, Apoptosis-related Cysteine Protease (CASP10, Accession NM_032976) is a VGAM24 host target gene. CASP10 BINDING SITE1 and CASP10 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by CASP10, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the com-

plementarity of the nucleotide sequences of CASP10 BINDING SITE1 and CASP10 BINDING SITE2, designated SEQ ID:223 and SEQ ID:224 respectively, to the nucleotide sequence of VGAM24 RNA, herein designated VGAM RNA, also designated SEQ ID:25.

[0719] A function of VGAM24 is therefore inhibition of Caspase 10, Apoptosis-related Cysteine Protease (CASP10, Accession NM_032976), a gene which is one aspartate-specific cysteine protease and important in death receptor signaling or other cellular processes. Accordingly, utilities of VGAM24 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CASP10. The function of CASP10 has been established by previous studies. Wang et al. (2001) showed that caspase-10 can function independently of caspase-8 in initiating FAS- and tumor necrosis factor-related apoptosis-inducing ligand-receptor-mediated apoptosis. Moreover, FAS crosslinking in primary human T cells leads to the recruitment and activation of caspase-10. They showed that the death-effector domains of caspases 8 and 10 interact with the death-effector domain of FADD. Nonetheless, they found that caspases 8 and 10 may have different apoptosis substrates and therefore potentially distinct roles in death re-

ceptor signaling or other cellular processes. By a candidate gene mutation search strategy, Wang et al. (1999) identified independent missense mutations in the CASP10 gene in 2 kindreds with type II autoimmune lymphoproliferative syndrome (ALPS2; 603909) characterized by abnormal lymphocyte and dendritic cell homeostasis and immune regulatory defects. The mutations (601762.0001 and 601762.0002) resulted in amino acid substitutions that decreased caspase activity and interfered with death receptor-induced apoptosis, particularly that stimulated by Fas ligand (OMIM Ref. No. 134638) and TRAIL (OMIM Ref. No. 603598). These results provided evidence that inherited nonlethal caspase abnormalities cause pleiotropic apoptosis defects underlying autoimmunity in ALPS2. To explore the possibility that mutation in the CASP10 gene might be involved in the development of non-Hodgkin lymphoma (NHL; 605027), Shin et al. (2002) analyzed the entire coding region and all splice sites of the CASP10 gene for the detection of somatic mutations in 117 human NHLs. Seventeen NHLs (14.5%) had CASP10 mutations, of which 3 were identified in the coding regions of the prodomain, 11 in the p17 large protease subunit, and 3 in the p12 small protease subunit. There

were 2 frameshift mutations and 1 nonsense mutation; the remaining 14 were missense mutations. Shin et al. (2002) expressed the tumor-derived CASP10 mutants in 293 cells and found that apoptosis was suppressed. These data suggested that the inactivating mutations of the CASP10 gene may lead to the loss of its apoptotic function and contribute to the pathogenesis of some human NHLs.

[0720] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0721] Wang, J.; Chun, H. J.; Wong, W.; Spencer, D. M.; Lenardo, M. J. : Caspase-10 is an initiator caspase in death receptor signaling. Proc. Nat. Acad. Sci. 98: 13884-13888, 2001. ; and

[0722] Wang, J.; Zheng, L.; Lobito, A.; Chan, F. K.; Dale, J.; Sneller, M.; Yao, X.; Puck, J. M.; Straus, S. E.; Lenardo, M. J. : Inherited human caspase 10 mutations underlie defective lympho.

[0723] Further studies establishing the function and utilities of CASP10 are found in John Hopkins OMIM database record ID 601762, and in cited publications numbered 315-298 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. LanC Lantibiotic

Synthetase Component C-like 1 (bacterial) (LANCL1, Accession NM_006055) is another VGAM24 host target gene. LANCL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LANCL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LANCL1 BINDING SITE, designated SEQ ID:100, to the nucleotide sequence of VGAM24 RNA, herein designated VGAM RNA, also designated SEQ ID:25.

[0724] Another function of VGAM24 is therefore inhibition of LanC Lantibiotic Synthetase Component C-like 1 (bacterial) (LANCL1, Accession NM_006055), a gene which binds the C-terminus of stomatin. Accordingly, utilities of VGAM24 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LANCL1. The function of LANCL1 has been established by previous studies. By affinity chromatography of solubilized human erythrocyte membrane proteins, Mayer et al. (1998) identified p40, a 40-kD protein that interacts with the C-terminus of the membrane protein stomatin (OMIM Ref. No. 133090). They used the sequence of p40 peptides to identify partial cDNAs in an EST database, and then cloned

cDNAs corresponding to the entire coding region using a PCR strategy. The predicted 399-amino acid protein contains the characteristic features of G protein-coupled receptors (GPCRs), including 7 transmembrane domains. Northern blot analysis revealed that p40 is expressed as a major 4.8-kb mRNA and as a minor 1.9-kb mRNA in all tissues. Dot blot experiments indicated that the highest levels of expression were in brain, spinal cord, testis, pituitary gland, and kidney. Using in situ hybridization to monkey tissues, Mayer et al. (1998) determined that p40 is expressed at high levels in neurons of the brain and spinal cord, in thymocytes, megakaryocytes, and macrophages. Bauer et al. (2000) determined that LANCL1 is not an integral membrane protein, but rather a weakly associated peripheral membrane protein, and is not a GPCR. They found that LANCL1 contains 7 highly conserved hydrophobic repeats and may play a role in peptide modification. Western blot analysis showed that LANCL1 is mainly expressed in brain, testis, ovary, and kidney. Mayer et al. (2001) determined that the human and mouse LANCL1 genes span 45 kb and 38 kb, respectively, each comprising 10 exons

[0725] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

- [0726] Bauer, H.; Mayer, H.; Marchler-Bauer, A.; Salzer, U.; Prohaska, R. : Characterization of p40/GPR69A as a peripheral membrane protein related to the lantibiotic synthetase component C. *Biochem. Biophys. Res. Commun.* 275: 69–74, 2000. ; and
- [0727] Mayer, H.; Bauer, H.; Prohaska, R. : Organization and chromosomal localization of the human and mouse genes coding for LanC-like protein 1 (LANCL1). *Cytogenet. Cell Genet.* 93: 100–104.
- [0728] Further studies establishing the function and utilities of LANCL1 are found in John Hopkins OMIM database record ID 604155, and in cited publications numbered 9–11 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Membrane-spanning 4-domains, Subfamily A, Member 3 (hematopoietic cell-specific) (MS4A3, Accession NM_006138) is another VGAM24 host target gene. MS4A3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MS4A3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of MS4A3 BINDING SITE, designated SEQ ID:101, to the nucleotide sequence of VGAM24 RNA, herein designated VGAM RNA, also designated SEQ ID:25.

- [0729] Another function of VGAM24 is therefore inhibition of Membrane-spanning 4-domains, Subfamily A, Member 3 (hematopoietic cell-specific) (MS4A3, Accession NM_006138). Accordingly, utilities of VGAM24 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MS4A3. Solute Carrier Family 1 (glutamate/neutral amino acid transporter), Member 4 (SLC1A4, Accession NM_003038) is another VGAM24 host target gene. SLC1A4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC1A4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC1A4 BINDING SITE, designated SEQ ID:64, to the nucleotide sequence of VGAM24 RNA, herein designated VGAM RNA, also designated SEQ ID:25.
- [0730] Another function of VGAM24 is therefore inhibition of Solute Carrier Family 1 (glutamate/neutral amino acid transporter), Member 4 (SLC1A4, Accession NM_003038), a

gene which transports alanine, serine, cysteine, and threonine. exhibits sodium dependence. Accordingly, utilities of VGAM24 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC1A4. The function of SLC1A4 has been established by previous studies. In a screening for cDNAs encoding proteins similar to the sodium-coupled glutamate transporter GLAST1, Hofmann et al. (1994) isolated a cDNA clone encoding a protein that turned out to be identical to the neutral amino acid transporter ASCT1 (Arriza et al., 1993; Shafqat et al., 1993). The new member of the GLAST-related transporter family did not transport glutamate or aspartate but alanine, serine, cysteine, and threonine instead. The open reading frame of 1,572 basepairs encodes 524 amino acid residues distributed over 8 exons spanning at least 40 kb of genomic DNA. The gene for ASCT1, designated SLC1A4, was assigned to 2p15-p13 by fluorescence in situ hybridization. The gene structure was not related to any previously characterized transporter gene. Zerangue and Kavanaugh (1996) found that the ASCT1 transporter functions primarily as an amino acid exchanger. Transport is associated with a chloride channel activity that is thermodynamically uncoupled from

amino acid transport.

- [0731] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:
- [0732] Arriza, J. L.; Kavanaugh, M. P.; Fairman, W. A.; Wu, Y.-N.; Murdoch, G. H.; North, R. A.; Amara, S. G. : Cloning and expression of a human neutral amino acid transporter with structural similarity to the glutamate transporter gene family. *J. Biol. Chem.* 268: 15329–15332, 1993. ; and
- [0733] Zerangue, N.; Kavanaugh, M. P. : ASCT–1 is a neutral amino acid exchanger with chloride channel activity. *J. Biol. Chem.* 271: 27991–27994, 1996.
- [0734] Further studies establishing the function and utilities of SLC1A4 are found in John Hopkins OMIM database record ID 600229, and in cited publications numbered 390–393 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Allantoicase (ALLC, Accession NM_018436) is another VGAM24 host target gene. ALLC BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by ALLC, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Ta–

ble 2 illustrates the complementarity of the nucleotide sequences of ALLC BINDING SITE, designated SEQ ID:162, to the nucleotide sequence of VGAM24 RNA, herein designated VGAM RNA, also designated SEQ ID:25.

[0735] Another function of VGAM24 is therefore inhibition of Allantoicase (ALLC, Accession NM_018436). Accordingly, utilities of VGAM24 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ALLC. Apolipoprotein L, 6 (APOL6, Accession NM_030641) is another VGAM24 host target gene. APOL6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by APOL6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of APOL6 BINDING SITE, designated SEQ ID:206, to the nucleotide sequence of VGAM24 RNA, herein designated VGAM RNA, also designated SEQ ID:25.

[0736] Another function of VGAM24 is therefore inhibition of Apolipoprotein L, 6 (APOL6, Accession NM_030641). Accordingly, utilities of VGAM24 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APOL6. Chromobox Homolog 6 (CBX6, Ac-

cession NM_014292) is another VGAM24 host target gene. CBX6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CBX6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CBX6 BINDING SITE, designated SEQ ID:128, to the nucleotide sequence of VGAM24 RNA, herein designated VGAM RNA, also designated SEQ ID:25.

[0737] Another function of VGAM24 is therefore inhibition of Chromobox Homolog 6 (CBX6, Accession NM_014292). Accordingly, utilities of VGAM24 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CBX6. FLJ10055 (Accession NM_017983) is another VGAM24 host target gene. FLJ10055 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10055, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10055 BINDING SITE, designated SEQ ID:156, to the nucleotide sequence of VGAM24 RNA, herein designated VGAM RNA, also designated SEQ ID:25.

[0738] Another function of VGAM24 is therefore inhibition of FLJ10055 (Accession NM_017983). Accordingly, utilities of VGAM24 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10055. FLJ22059 (Accession NM_022752) is another VGAM24 host target gene. FLJ22059 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ22059, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22059 BINDING SITE, designated SEQ ID:191, to the nucleotide sequence of VGAM24 RNA, herein designated VGAM RNA, also designated SEQ ID:25.

[0739] Another function of VGAM24 is therefore inhibition of FLJ22059 (Accession NM_022752). Accordingly, utilities of VGAM24 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22059. Potassium Voltage-gated Channel, Subfamily H (eag-related), Member 8 (KCNH8, Accession NM_144633) is another VGAM24 host target gene. KCNH8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KCNH8, corresponding to a

HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCNH8 BINDING SITE, designated SEQ ID:252, to the nucleotide sequence of VGAM24 RNA, herein designated VGAM RNA, also designated SEQ ID:25.

[0740] Another function of VGAM24 is therefore inhibition of Potassium Voltage-gated Channel, Subfamily H (eag-related), Member 8 (KCNH8, Accession NM_144633). Accordingly, utilities of VGAM24 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNH8. KIAA0870 (Accession XM_088315) is another VGAM24 host target gene. KIAA0870 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0870, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0870 BINDING SITE, designated SEQ ID:339, to the nucleotide sequence of VGAM24 RNA, herein designated VGAM RNA, also designated SEQ ID:25.

[0741] Another function of VGAM24 is therefore inhibition of KIAA0870 (Accession XM_088315). Accordingly, utilities

of VGAM24 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0870. KIAA1157 (Accession XM_051093) is another VGAM24 host target gene. KIAA1157 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1157, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1157 BINDING SITE, designated SEQ ID:296, to the nucleotide sequence of VGAM24 RNA, herein designated VGAM RNA, also designated SEQ ID:25.

[0742] Another function of VGAM24 is therefore inhibition of KIAA1157 (Accession XM_051093). Accordingly, utilities of VGAM24 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1157. PRO1048 (Accession NM_018497) is another VGAM24 host target gene. PRO1048 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PRO1048, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO1048 BINDING

SITE, designated SEQ ID:163, to the nucleotide sequence of VGAM24 RNA, herein designated VGAM RNA, also designated SEQ ID:25.

[0743] Another function of VGAM24 is therefore inhibition of PRO1048 (Accession NM_018497). Accordingly, utilities of VGAM24 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO1048. PRO1787 (Accession NM_018606) is another VGAM24 host target gene. PRO1787 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRO1787, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO1787 BINDING SITE, designated SEQ ID:165, to the nucleotide sequence of VGAM24 RNA, herein designated VGAM RNA, also designated SEQ ID:25.

[0744] Another function of VGAM24 is therefore inhibition of PRO1787 (Accession NM_018606). Accordingly, utilities of VGAM24 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO1787. Ubiquitin-conjugating Enzyme E2G 1 (UBC7 homolog, C. elegans) (UBE2G1, Accession NM_003342) is another

VGAM24 host target gene. UBE2G1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UBE2G1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UBE2G1 BINDING SITE, designated SEQ ID:67, to the nucleotide sequence of VGAM24 RNA, herein designated VGAM RNA, also designated SEQ ID:25.

[0745] Another function of VGAM24 is therefore inhibition of Ubiquitin-conjugating Enzyme E2G 1 (UBC7 homolog, *C. elegans*) (UBE2G1, Accession NM_003342). Accordingly, utilities of VGAM24 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBE2G1. LOC122402 (Accession XM_058619) is another VGAM24 host target gene. LOC122402 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC122402, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC122402 BINDING SITE, designated SEQ ID:306, to the nucleotide sequence of VGAM24 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:25.

[0746] Another function of VGAM24 is therefore inhibition of LOC122402 (Accession XM_058619). Accordingly, utilities of VGAM24 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC122402. LOC153592 (Accession XM_098396) is another VGAM24 host target gene. LOC153592 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC153592, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153592 BINDING SITE, designated SEQ ID:355, to the nucleotide sequence of VGAM24 RNA, herein designated VGAM RNA, also designated SEQ ID:25.

[0747] Another function of VGAM24 is therefore inhibition of LOC153592 (Accession XM_098396). Accordingly, utilities of VGAM24 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153592. LOC256158 (Accession XM_175125) is another VGAM24 host target gene. LOC256158 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC256158, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256158 BINDING SITE, designated SEQ ID:404, to the nucleotide sequence of VGAM24 RNA, herein designated VGAM RNA, also designated SEQ ID:25.

[0748] Another function of VGAM24 is therefore inhibition of LOC256158 (Accession XM_175125). Accordingly, utilities of VGAM24 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256158. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 25 (VGAM25) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0749] VGAM25 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM25 was detected is described hereinabove with reference to Figs. 1–8.

[0750] VGAM25 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Immunodeficiency

ciency Virus 1. VGAM25 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0751] VGAM25 gene encodes a VGAM25 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM25 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM25 precursor RNA is designated SEQ ID:11, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:11 is located at position 9080 relative to the genome of Human Immunodeficiency Virus 1.

[0752] VGAM25 precursor RNA folds onto itself, forming VGAM25 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0753] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM25 folded precursor RNA into VGAM25 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 90%) nucleotide sequence of VGAM25 RNA is designated SEQ ID:26, and is provided hereinbelow with reference to the sequence listing part.

[0754] VGAM25 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM25 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM25 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[0755] VGAM25 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM25 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide

sequence of VGAM25 RNA is an accurate or a partial inverted-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM25 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM25 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[0756] The complementary binding of VGAM25 RNA, herein designated VGAM RNA, to host target binding sites on VGAM25 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM25 host target RNA into VGAM25 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target

protein is therefore outlined by a broken line.

[0757] It is appreciated that VGAM25 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM25 host target genes. The mRNA of each one of this plurality of VGAM25 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM25 RNA, herein designated VGAM RNA, and which when bound by VGAM25 RNA causes inhibition of translation of respective one or more VGAM25 host target proteins.

[0758] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM25 gene, herein designated VGAM GENE, on one or more VGAM25 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression

of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[0759] It is yet further appreciated that a function of VGAM25 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM25 include diagnosis, prevention and treatment of viral infection by Human Immunodeficiency Virus 1. Specific functions, and accordingly utilities, of VGAM25 correlate with, and may be deduced from, the identity of the host target genes which VGAM25 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0760] Nucleotide sequences of the VGAM25 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM25 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM25 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM25 are further described hereinbelow with reference to Table 1.

[0761] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of

Fig. 1, found on VGAM25 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM25 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0762] As mentioned hereinabove with reference to Fig. 1, a function of VGAM25 gene, herein designated VGAM is inhibition of expression of VGAM25 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM25 correlate with, and may be deduced from, the identity of the target genes which VGAM25 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[0763] Integrin, Alpha 5 (fibronectin receptor, alpha polypeptide) (ITGA5, Accession XM_028642) is a VGAM25 host target gene. ITGA5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ITGA5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ITGA5 BINDING SITE, designated SEQ ID:264, to the nucleotide sequence of VGAM25 RNA, herein designated VGAM RNA, also designated SEQ ID:26.

[0764] A function of VGAM25 is therefore inhibition of Integrin, Alpha 5 (fibronectin receptor, alpha polypeptide) (ITGA5, Accession XM_028642), a gene which is receptor for fibronectin and fibrinogen and recognizes the sequence r-g-d in its ligands. Accordingly, utilities of VGAM25 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ITGA5. The function of ITGA5 has been established by previous studies. The fibronectin receptor, a member of the integrin family of heterodimeric glycopeptides, mediates the binding of cells to fibronectin substrata. To study the structure of the receptor, Argraves et al. (1986) isolated cDNA clones coding for the alpha subunit from a placental cDNA library. The cDNAs code for 229 amino acids from the C-terminus of the alpha subunit. The deduced sequence had a hydrophobic region with properties characteristic of a membrane-spanning domain. Argraves et al. (1987) deduced the amino acid sequence from cDNA. The alpha subunit, which is processed into 2 polypeptides disulfide-bonded to one another, has 1,008 amino acids; the beta subunit has 778 amino acids. Fitzgerald et al. (1987) presented comparisons of the cDNA-derived protein sequences of fibronectin receptor, vitronectin receptor (OMIM Ref. No.

193210), and platelet glycoprotein IIb (OMIM Ref. No. 273800). Sosnoski et al. (1988) assigned the FNRA gene to 12q11–q13 by Southern analysis of somatic cell hybrid DNA. Location on chromosome 12 was confirmed by Spurr and Rooke (1991) by study of human/rodent somatic cell hybrids. Krissansen et al. (1992) pointed out the possible significance of the fact that a related gene coding for integrin beta–7 subunit (ITGB7; 147559) is also located on chromosome 12. Adkison et al. (1994) mapped the murine homolog, Itga5, to chromosome 15, distal to D15Mit16, by analysis of DNA from an interspecific back–cross

[0765] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0766] Adkison, L. R.; White, R. A.; Haney, D. M.; Lee, J. C.; Pusey, K. T.; Gardner, J. : The fibronectin receptor, alpha subunit (Itga5) maps to murine chromosome 15, distal to D15Mit16. Mammalian Genome 5: 456–457, 1994. ; and

[0767] Argraves, W. S.; Pytela, R.; Suzuki, S.; Millan, J. L.; Pierschbacher, M. D.; Ruoslahti, E. : cDNA sequences from the alpha subunit of the fibronectin receptor predict a trans–membrane d.

[0768] Further studies establishing the function and utilities of ITGA5 are found in John Hopkins OMIM database record ID 135620, and in cited publications numbered 135–141 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Splicing Factor 3b, Subunit 3, 130kDa (SF3B3, Accession NM_012426) is another VGAM25 host target gene. SF3B3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SF3B3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SF3B3 BINDING SITE, designated SEQ ID:116, to the nucleotide sequence of VGAM25 RNA, herein designated VGAM RNA, also designated SEQ ID:26.

[0769] Another function of VGAM25 is therefore inhibition of Splicing Factor 3b, Subunit 3, 130kDa (SF3B3, Accession NM_012426). Accordingly, utilities of VGAM25 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SF3B3. Solute Carrier Family 4, Sodium Bicarbonate Cotransporter, Member 4 (SLC4A4, Accession NM_003759) is another VGAM25 host target gene. SLC4A4 BINDING SITE is HOST TARGET binding site

found in the 3' untranslated region of mRNA encoded by SLC4A4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC4A4 BINDING SITE, designated SEQ ID:71, to the nucleotide sequence of VGAM25 RNA, herein designated VGAM RNA, also designated SEQ ID:26.

[0770] Another function of VGAM25 is therefore inhibition of Solute Carrier Family 4, Sodium Bicarbonate Cotransporter, Member 4 (SLC4A4, Accession NM_003759), a gene which is a sodium bicarbonate cotransporter. Accordingly, utilities of VGAM25 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC4A4. The function of SLC4A4 has been established by previous studies. By screening a human heart cDNA library with rat kidney Nbc cDNAs, followed by a PCR approach, Choi et al. (1999) isolated a full-length cDNA encoding a heart NBC, which they called hhNBC. They reported that the coding sequence of hhNBC is identical to that of pNBC (Abuladze et al., 1998). However, the 5-prime untranslated regions of hhNBC and pNBC differ. Northern blot analysis using the 5-prime region of the hhNBC coding sequence as probe detected an approximately 9-kb tran-

script that was strongly expressed in pancreas and weakly expressed in heart and brain. Choi et al. (1999) found that both hhNBC and kNBC (Burnham et al., 1997), when expressed in *Xenopus*, are electrogenic. Soleimani and Burnham (2000) stated that kNBC (Burnham et al., 1997) and pNBC (Abuladze et al., 1998) are encoded by splice variants of the same gene, SLC4A4, which they called NBC1. Mutations in the SLC4A4 gene (e.g., 603345.0001, 603345.0002) cause proximal renal tubular acidosis with bilateral glaucoma, cataracts, and band keratopathy (OMIM Ref. No. 604278). Such mutations may increase the bicarbonate concentration in the corneal stroma, which would facilitate calcium deposition leading to band keratopathy. Igarashi et al. (1999) suggested that the kidney and pancreatic NBCs are derived from a common gene by alternative splicing and that mutations at the common region would inactivate both isoforms. Studies by Usui et al. (1999) confirmed that both kidney and pancreatic NBC are involved in the transport of sodium and bicarbonate out of the corneal stroma and into the aqueous humor.

[0771] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

- [0772] Soleimani, M.; Burnham, C. E. : Physiologic and molecular aspects of the Na(+):HCO(3-) cotransporter in health and disease processes. *Kidney Int.* 57: 371–384, 2000. ; and
- [0773] Choi, I.; Romero, M. F.; Khandoudi, N.; Bril, A.; Boron, W. F. : Cloning and characterization of a human electrogenic Na(+)-HCO(3-) cotransporter isoform (hhNBC). *Am. J. Physiol.* 276: C57.
- [0774] Further studies establishing the function and utilities of SLC4A4 are found in John Hopkins OMIM database record ID 603345, and in cited publications numbered 426–432 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Zinc Finger Protein 180 (HHZ168) (ZNF180, Accession NM_013256) is another VGAM25 host target gene. ZNF180 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF180, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF180 BINDING SITE, designated SEQ ID:120, to the nucleotide sequence of VGAM25 RNA, herein designated VGAM RNA, also designated SEQ ID:26.
- [0775] Another function of VGAM25 is therefore inhibition of Zinc

Finger Protein 180 (HHZ168) (ZNF180, Accession NM_013256). Accordingly, utilities of VGAM25 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF180. Adaptor-related Protein Complex 1, Gamma 2 Subunit (AP1G2, Accession NM_080545) is another VGAM25 host target gene. AP1G2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by AP1G2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AP1G2 BINDING SITE, designated SEQ ID:233, to the nucleotide sequence of VGAM25 RNA, herein designated VGAM RNA, also designated SEQ ID:26.

[0776] Another function of VGAM25 is therefore inhibition of Adaptor-related Protein Complex 1, Gamma 2 Subunit (AP1G2, Accession NM_080545). Accordingly, utilities of VGAM25 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AP1G2. BCL2-like 1 (BCL2L1, Accession NM_138578) is another VGAM25 host target gene. BCL2L1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BCL2L1, corresponding to a HOST

TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCL2L1 BINDING SITE, designated SEQ ID:241, to the nucleotide sequence of VGAM25 RNA, herein designated VGAM RNA, also designated SEQ ID:26.

[0777] Another function of VGAM25 is therefore inhibition of BCL2-like 1 (BCL2L1, Accession NM_138578). Accordingly, utilities of VGAM25 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCL2L1. FLJ25012 (Accession NM_144592) is another VGAM25 host target gene. FLJ25012 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ25012, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ25012 BINDING SITE, designated SEQ ID:250, to the nucleotide sequence of VGAM25 RNA, herein designated VGAM RNA, also designated SEQ ID:26.

[0778] Another function of VGAM25 is therefore inhibition of FLJ25012 (Accession NM_144592). Accordingly, utilities of VGAM25 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with FLJ25012. FLJ31952 (Accession NM_144682) is another VGAM25 host target gene. FLJ31952 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ31952, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ31952 BINDING SITE, designated SEQ ID:253, to the nucleotide sequence of VGAM25 RNA, herein designated VGAM RNA, also designated SEQ ID:26.

[0779] Another function of VGAM25 is therefore inhibition of FLJ31952 (Accession NM_144682). Accordingly, utilities of VGAM25 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ31952. MDS025 (Accession NM_021825) is another VGAM25 host target gene. MDS025 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MDS025, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MDS025 BINDING SITE, designated SEQ ID:184, to the nucleotide sequence of

VGAM25 RNA, herein designated VGAM RNA, also designated SEQ ID:26.

[0780] Another function of VGAM25 is therefore inhibition of MDS025 (Accession NM_021825). Accordingly, utilities of VGAM25 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MDS025. MGC32043 (Accession NM_144582) is another VGAM25 host target gene. MGC32043 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC32043, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC32043 BINDING SITE, designated SEQ ID:249, to the nucleotide sequence of VGAM25 RNA, herein designated VGAM RNA, also designated SEQ ID:26.

[0781] Another function of VGAM25 is therefore inhibition of MGC32043 (Accession NM_144582). Accordingly, utilities of VGAM25 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC32043. Musashi Homolog 2 (Drosophila) (MSI2, Accession NM_138962) is another VGAM25 host target gene. MSI2 BINDING SITE is HOST TARGET binding site found in

the 3` untranslated region of mRNA encoded by MSI2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MSI2 BINDING SITE, designated SEQ ID:245, to the nucleotide sequence of VGAM25 RNA, herein designated VGAM RNA, also designated SEQ ID:26.

[0782] Another function of VGAM25 is therefore inhibition of Musashi Homolog 2 (Drosophila) (MSI2, Accession NM_138962). Accordingly, utilities of VGAM25 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MSI2. Zinc Finger Protein 271 (ZNF271, Accession XM_170865) is another VGAM25 host target gene. ZNF271 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by ZNF271, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF271 BINDING SITE, designated SEQ ID:395, to the nucleotide sequence of VGAM25 RNA, herein designated VGAM RNA, also designated SEQ ID:26.

[0783] Another function of VGAM25 is therefore inhibition of Zinc

Finger Protein 271 (ZNF271, Accession XM_170865). Accordingly, utilities of VGAM25 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF271. LOC144508 (Accession XM_101073) is another VGAM25 host target gene. LOC144508 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC144508, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144508 BINDING SITE, designated SEQ ID:362, to the nucleotide sequence of VGAM25 RNA, herein designated VGAM RNA, also designated SEQ ID:26.

[0784] Another function of VGAM25 is therefore inhibition of LOC144508 (Accession XM_101073). Accordingly, utilities of VGAM25 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144508. LOC145845 (Accession XM_096884) is another VGAM25 host target gene. LOC145845 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145845, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145845 BINDING SITE, designated SEQ ID:346, to the nucleotide sequence of VGAM25 RNA, herein designated VGAM RNA, also designated SEQ ID:26.

[0785] Another function of VGAM25 is therefore inhibition of LOC145845 (Accession XM_096884). Accordingly, utilities of VGAM25 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145845. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 26 (VGAM26) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0786] VGAM26 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM26 was detected is described hereinabove with reference to Figs. 1–8.

[0787] VGAM26 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Immunodeficiency Virus 1. VGAM26 host target gene, herein desig-

nated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0788] VGAM26 gene encodes a VGAM26 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM26 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM26 precursor RNA is designated SEQ ID:12, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:12 is located at position 2049 relative to the genome of Human Immunodeficiency Virus 1.

[0789] VGAM26 precursor RNA folds onto itself, forming VGAM26 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0790] An enzyme complex designated DICER COMPLEX, `dices` the VGAM26 folded precursor RNA into VGAM26 RNA,

herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 72%) nucleotide sequence of VGAM26 RNA is designated SEQ ID:27, and is provided hereinbelow with reference to the sequence listing part.

[0791] VGAM26 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM26 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM26 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[0792] VGAM26 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM26 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM26 RNA is an accurate or a partial in-

versed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM26 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM26 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[0793] The complementary binding of VGAM26 RNA, herein designated VGAM RNA, to host target binding sites on VGAM26 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM26 host target RNA into VGAM26 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0794] It is appreciated that VGAM26 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM26 host target genes. The mRNA of each one of this plurality of VGAM26 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM26 RNA, herein designated VGAM RNA, and which when bound by VGAM26 RNA causes inhibition of translation of respective one or more VGAM26 host target proteins.

[0795] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM26 gene, herein designated VGAM GENE, on one or more VGAM26 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although spe-

cific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[0796] It is yet further appreciated that a function of VGAM26 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM26 include diagnosis, prevention and treatment of viral infection by Human Immunodeficiency Virus 1. Specific functions, and accordingly utilities, of VGAM26 correlate with, and may be deduced from, the identity of the host target genes which VGAM26 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0797] Nucleotide sequences of the VGAM26 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM26 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM26 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM26 are further described hereinbelow with reference to Table 1.

[0798] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM26 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM26 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0799] As mentioned hereinabove with reference to Fig. 1, a function of VGAM26 gene, herein designated VGAM is inhibition of expression of VGAM26 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM26 correlate with, and may be deduced from, the identity of the target genes which VGAM26 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[0800] Cadherin 19, Type 2 (CDH19, Accession NM_021153) is a VGAM26 host target gene. CDH19 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CDH19, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CDH19 BINDING SITE, designated SEQ ID:182, to the nucleotide sequence of VGAM26 RNA, herein designated VGAM RNA, also designated SEQ ID:27.

[0801] A function of VGAM26 is therefore inhibition of Cadherin

19, Type 2 (CDH19, Accession NM_021153), a gene which is a calcium dependent cell adhesion protein. Accordingly, utilities of VGAM26 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CDH19. The function of CDH19 has been established by previous studies. In EST database searches for cadherin sequences, Kools et al. (2000) identified a partial CDH19 cDNA, which they called CDH7L2. CDH19 encodes a 772-amino acid protein predicted to contain 5 EC (extracellular calcium-binding) repeats, a transmembrane domain, and a cytoplasmic tail. Kools et al. (2000) classified CDH19 as an atypical (type II) cadherin due to the lack of the HAV cell adhesion recognition sequence specific for classic cadherins. CDH19 was previously identified and named CDH7 by Kremmidiotis et al. (1998); however, phylogenetic analysis carried out by Kools et al. (2000) led to nomenclature corrections within the cadherin gene family. CDH19 shares significant homology with chicken Cdh7, but Kools et al. (2000) identified the newly designated CDH7 gene (OMIM Ref. No. 605806) as the likely human ortholog of chicken Cdh7. Using RT-PCR analysis, Kools et al. (2000) detected CDH19 expression in all tissues tested, with the exception of uterus. By somatic cell

hybrid analysis and fluorescence in situ hybridization, Kremmidiotis et al. (1998) mapped the human CDH19 gene to chromosome 18q22–q23. Using the same methods, Kools et al. (2000) mapped the CDH19 gene to the same location in a cluster with CDH7 (OMIM Ref. No. 605806) and CDH20 (OMIM Ref. No. 605807).

[0802] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0803] Kools, P.; Van Imschoot, G.; van Roy, F. : Characterization of three novel human cadherin genes (CDH7, CDH19, and CDH20) clustered on chromosome 18q22–q23 and with high homology to chicken cadherin–7. *Genomics* 68: 283–295, 2000. ; and

[0804] Kremmidiotis, G.; Baker, E.; Crawford, J.; Eyre, H. J.; Nahmias, J.; Callen, D. F. : Localization of human cadherin genes to chromosome regions exhibiting cancer–related loss of hetero.

[0805] Further studies establishing the function and utilities of CDH19 are found in John Hopkins OMIM database record ID 603016, and in cited publications numbered 43 and 604 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Crystallin,

Gamma S (CRYGS, Accession NM_017541) is another VGAM26 host target gene. CRYGS BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CRYGS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CRYGS BINDING SITE, designated SEQ ID:152, to the nucleotide sequence of VGAM26 RNA, herein designated VGAM RNA, also designated SEQ ID:27.

[0806] Another function of VGAM26 is therefore inhibition of Crystallin, Gamma S (CRYGS, Accession NM_017541), a gene which is a dominant structural components of the vertebrate eye lens. Accordingly, utilities of VGAM26 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CRYGS. The function of CRYGS has been established by previous studies. The beta-crystallins and gamma-crystallins of the mammalian lens form a superfamily of related proteins which are apparently derived from a common ancestral gene; see CRYGA (OMIM Ref. No. 123660). An exceptional member of this superfamily is gamma-S (formerly beta-S). In contrast to the beta-crystallins which associate in various

combinations to form low or high molecular weight aggregates, gamma-S is, like the other gamma-crystallins, a monomeric protein. It was suggested by den Dunnen et al. (1985) that all members of the human gamma-crystallin gene family are located on chromosome 2. However, study of hamster-human somatic cell hybrids with a bovine cDNA probe for CRYGS led Wijnen et al. (1989) to the conclusion that this gene is located on human chromosome 3.

[0807] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0808] den Dunnen, J. T.; Jongbloed, R. J. E.; Geurts van Kessel, A. H. M.; Schoenmakers, J. G. G. : Human lens gamma-crystallin sequences are located in the p12-qter region of chromosome 2. Hum. Genet. 70: 217-221, 1985. ; and

[0809] Wijnen, J. T.; Oldenburg, M.; Bloemendal, H.; Meera Khan, P. : GS(gamma-S)-crystallin (CRYGS) assignment to chromosome 3. (Abstract) Cytogenet. Cell Genet. 51: 1108 only, 1989.

[0810] Further studies establishing the function and utilities of CRYGS are found in John Hopkins OMIM database record ID 123730, and in cited publications numbered 615 listed

in the bibliography section hereinbelow, which are also hereby incorporated by reference. Cytochrome P450, Subfamily I (dioxin-inducible), Polypeptide 1 (glaucoma 3, primary infantile) (CYP1B1, Accession NM_000104) is another VGAM26 host target gene. CYP1B1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CYP1B1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CYP1B1 BINDING SITE, designated SEQ ID:33, to the nucleotide sequence of VGAM26 RNA, herein designated VGAM RNA, also designated SEQ ID:27.

[0811] Another function of VGAM26 is therefore inhibition of Cytochrome P450, Subfamily I (dioxin-inducible), Polypeptide 1 (glaucoma 3, primary infantile) (CYP1B1, Accession NM_000104), a gene which participates in the metabolism of a molecule that is a participant in eye development. Accordingly, utilities of VGAM26 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CYP1B1. The function of CYP1B1 has been established by previous studies. In the study of candidate genes identified in the critical region of 2p21 where a ma-

jor gene for primary congenital glaucoma, GLC3A (OMIM Ref. No. 231300), had been mapped by linkage studies, Stoilov et al. (1997) found the CYP1B1 gene, which had previously been identified by Sutter et al. (1994). From a determination of the intron/exon junctions of this gene, Stoilov et al. (1997) concluded that the gene contains 3 exons and 2 introns. The entire coding sequence of the genes is contained in exons 2 and 3. This genomic structure agreed with that reported by Tang et al. (1996). Screening for the presence of coding sequence changes in the CYP1B1 gene, Stoilov et al. (1997) identified 3 different truncating mutations: a 13-bp deletion found in 1 consanguineous and 1 nonconsanguineous family (601771.0001); a single cytosine insertion observed in another 2 consanguineous families (601771.0002); and a large deletion found in an additional consanguineous family. In addition, a G-to-C transversion at nucleotide 1640 of the CYP1B1 coding sequence was found that caused a val432-to-leu amino acid substitution. This change created an EcoR57 restriction site, thus providing a rapid screening method. Heterozygosity for the val432-to-leu change was found in 51.4% of 70 normal individuals. This amino acid change was not in that part of

CYP1B1 that represented conserved sequences, and both valine and leucine are neutral and hydrophobic. Their very similar aliphatic side groups differ by a single $-CH_2$ group. Therefore, this change appeared to represent a common amino acid polymorphism that is not related to the primary congenital glaucoma phenotype. Identification of CYP1B1 as the gene affected in primary congenital glaucoma was said by Stoilov et al. (1997) to be the first example in which mutations in a member of the cytochrome P450 superfamily results in a primary developmental defect. The finding was not unexpected, however, as a link between members of this superfamily and the processes of growth and differentiation had been postulated previously. They speculated that CYP1B1 participates in the metabolism of an as-yet-unknown biologically active molecule that is a participant in eye development. Stoilov et al. (1997) demonstrated that a stable protein product is produced in the affected subjects of these families, and that the 3 mutations they described would be expected to result in a product lacking between 189 and 254 amino acids from the C terminus. This segment harbors the invariant cysteine of all known cytochrome P450 amino sequences; in CYP1B1 it is cys470. Schwartzman et

al. (1987) implicated a cytochrome–P450–dependent arachidonate metabolite that inhibits Na⁺,K⁺–ATPase in the cornea in regulating corneal transparency and aqueous humor secretion. This finding is consistent with the clouding of the cornea and increased intraocular pressure, the 2 major diagnostic criteria for primary congenital glaucoma.

[0812] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0813] Bejjani, B. A.; Lewis, R. A.; Tomey, K. F.; Anderson, K. L.; Dueker, D. K.; Jabak, M.; Astle, W. F.; Otterud, B.; Leppert, M.; Lupski, J. R. : Mutations in CYP1B1, the gene for cytochrome P4501B1, are the predominant cause of primary congenital glaucoma in Saudi Arabia. Am. J. Hum. Genet. 62: 325–333, 1998. ; and

[0814] Stoilov, I.; Akarsu, A. N.; Alozie, I.; Child, A.; Barsoum–Homsy, M.; Turacli, M. E.; Or, M.; Lewis, R. A.; Ozdemir, N.; Brice, G.; Aktan, S. G.; Chevrette, L.; Coca–Prados, M.; Sarfara.

[0815] Further studies establishing the function and utilities of CYP1B1 are found in John Hopkins OMIM database record ID 601771, and in cited publications numbered 461–46

and 473–480 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. GLI–Kruppel Family Member GLI3 (Greig cephalopolysyndactyly syndrome) (GLI3, Accession NM_000168) is another VGAM26 host target gene. GLI3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by GLI3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GLI3 BINDING SITE, designated SEQ ID:35, to the nucleotide sequence of VGAM26 RNA, herein designated VGAM RNA, also designated SEQ ID:27.

[0816] Another function of VGAM26 is therefore inhibition of GLI–Kruppel Family Member GLI3 (Greig cephalopolysyndactyly syndrome) (GLI3, Accession NM_000168). Accordingly, utilities of VGAM26 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GLI3. Piccolo (presynaptic cytomatrix protein) (PCLO, Accession XM_168530) is another VGAM26 host target gene. PCLO BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PCLO, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCLO BINDING SITE, designated SEQ ID:391, to the nucleotide sequence of VGAM26 RNA, herein designated VGAM RNA, also designated SEQ ID:27.

[0817] Another function of VGAM26 is therefore inhibition of Piccolo (presynaptic cytomatrix protein) (PCLO, Accession XM_168530), a gene which involves in the cycling of synaptic vesicles. Accordingly, utilities of VGAM26 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCLO. The function of PCLO has been established by previous studies. Synaptic vesicles dock and fuse in the active zone of the plasma membrane at chemical synapses. The presynaptic cytoskeletal matrix (PCM), which is associated with the active zone and is situated between synaptic vesicles, is thought to be involved in maintaining the neurotransmitter release site in register with the postsynaptic reception apparatus. The cycling of synaptic vesicles is a multistep process involving a number of proteins (see OMIM Ref. No. 603215). Among the components of the PCM that orchestrate these events are Bassoon (BSN; 604020), RIM (RBBP8; 604124), Oboe, and Piccolo (PCLO). By searching EST and genome

databases with a murine Pclo cDNA probe, Fenster et al. (2000) identified genomic sequences and a brain-specific EST (KIAA0559) encoding human PCLO. The 5-prime terminus of the human sequence had yet to be determined, but the authors were able to deduce nearly the entire human PCLO protein. Sequence analysis indicated that the deduced 4,880-amino acid rat Pclo protein is 86% identical to human PCLO. In addition, PCLO shares significant amino acid sequence homology with BSN. BSN and PCLO share 10 homology regions, or PBH regions. PBH1 and PBH2 contain 2 double-zinc finger motifs. PBH4, PBH6, and PBH8 are likely to form coiled-coil structures. At the C terminus, unlike BSN but like RIM and Oboe, PCLO contains a PDZ domain and a C2 domain. The PCLO C2 domain contains all the asp residues required for calcium binding. Fenster et al. (2000) noted that PCLO also contains multiple proline-rich segments. Confocal microscopy analysis of cultured hippocampal neurons showed colocalization of BSN and PCLO at identical GABAergic and glutamergic synapses, of synaptotagmin (see OMIM Ref. No. SYT1; 185605) and PCLO along dendritic profiles, and of PCLO zinc fingers and PRA1 (OMIM Ref. No. 604925) at nerve terminals.

- [0818] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:
- [0819] Fenster, S. D.; Chung, W. J.; Zhai, R.; Cases–Langhoff, C.; Voss, B.; Garner, A. M.; Kaempfer, U.; Kindler, S.; Gundelfinger, E. D.; Garner, C. C. : Piccolo, a presynaptic zinc finger protein structurally related to Bassoon. *Neuron* 25: 203–214, 2000. ; and
- [0820] Nagase, T.; Ishikawa, K.; Miyajima, N.; Tanaka, A.; Kotani, H.; Nomura, N.; Ohara, O. : Prediction of the coding sequences of unidentified human genes. IX. The complete sequences of 10.
- [0821] Further studies establishing the function and utilities of PCLO are found in John Hopkins OMIM database record ID 604918, and in cited publications numbered 19 and 299 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Protein Phosphatase 2, Regulatory Subunit B (B56), Alpha Isoform (PPP2R5A, Accession NM_006243) is another VGAM26 host target gene. PPP2R5A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PPP2R5A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP2R5A BINDING SITE, designated SEQ ID:102, to the nucleotide sequence of VGAM26 RNA, herein designated VGAM RNA, also designated SEQ ID:27.

[0822] Another function of VGAM26 is therefore inhibition of Protein Phosphatase 2, Regulatory Subunit B (B56), Alpha Isoform (PPP2R5A, Accession NM_006243), a gene which is a regulatory subunit of protein phosphatase 2A. Accordingly, utilities of VGAM26 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPP2R5A. The function of PPP2R5A has been established by previous studies. Protein phosphorylation is a regulatory mechanism commonly employed in cellular processes such as cell cycle progression, growth factor signaling, and cell transformation. Protein phosphatase 2A (PP2A), a heterotrimeric serine/threonine phosphatase, has been implicated in a variety of regulatory processes including cell growth and division, muscle contraction, and gene transcription. PP2A is a trimeric enzyme composed of a catalytic subunit (OMIM Ref. No. 176915), a structural subunit, and any of several different regulatory subunits which control its specificity. One family of re-

lated PP2A regulatory subunits is designated the B56 family and contains at least 5 different members (McCright and Virshup (1995)). The alpha subunit gene encodes a cytoplasmic phosphoprotein. The alpha and gamma (OMIM Ref. No. 601645) subunits are expressed at highest levels in skeletal and cardiac muscle. See also the entries describing the beta (OMIM Ref. No. 601644), delta (OMIM Ref. No. 601646), and epsilon (OMIM Ref. No. 601647) subunits. McCright et al. (1996) mapped the gene for the alpha subunit, designated PPP2R5A, to 1q41 by fluorescence in situ hybridization.

[0823] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0824] McCright, B.; Brothman, A. R.; Virshup, D. M. : Assignment of human protein phosphatase 2A regulatory subunit genes B56-alpha, B56-beta, B56-gamma, B56-delta, and B56-epsilon (PPP2R5A--PPP2R5E), highly expressed in muscle and brain, to chromosome regions 1q41, 11q12, 3p21, 6p21.1, and 7p11.2-to-p12. Genomics 36: 168-170, 1996. ; and

[0825] McCright, B.; Virshup, D. M. : Identification of a new family of protein phosphatase 2A regulatory subunits. J. Biol.

Chem. 270: 26123–26128, 1995.

[0826] Further studies establishing the function and utilities of PPP2R5A are found in John Hopkins OMIM database record ID 601643, and in cited publications numbered 291–292 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Phosphotriesterase Related (PTER, Accession NM_030664) is another VGAM26 host target gene. PTER BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PTER, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTER BINDING SITE, designated SEQ ID:207, to the nucleotide sequence of VGAM26 RNA, herein designated VGAM RNA, also designated SEQ ID:27.

[0827] Another function of VGAM26 is therefore inhibition of Phosphotriesterase Related (PTER, Accession NM_030664), a gene which is a phosphotriesterase homology protein. Accordingly, utilities of VGAM26 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTER. The function of PTER has been established by previous studies. Microbial phosphotriesterases are a group of zinc metalloenzymes that cat-

alyze the hydrolysis of a range of phosphotriester compounds. Davies et al. (1997) isolated rat cDNAs encoding a phosphotriesterase homolog, which they named rpr1. Using a rat rpr1 cDNA as a hybridization probe, Alimova-Kost et al. (1998) isolated human genomic sequences of PTER, a homolog of phosphotriesterases. By FISH, Alimova-Kost et al. (1998) mapped the human PTER gene to 10p12

[0828] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0829] Alimova-Kost, M. V.; Imreh, S.; Buchman, V. L.; Ninkina, N. N. : Assignment of phosphotriesterase-related gene (PTER) to human chromosome band 10p12 by in situ hybridization. Cytogenet. Cell Genet. 83: 16-17, 1998. ; and

[0830] Davies, J. A.; Buchman, V. L.; Krylova, O.; Ninkina, N. N. : Molecular cloning and expression pattern of rpr-1, a resiniferatoxin-binding, phosphotriesterase-related protein, expressed.

[0831] Further studies establishing the function and utilities of PTER are found in John Hopkins OMIM database record ID 604446, and in cited publications numbered 44-45 listed in the bibliography section hereinbelow, which are also

hereby incorporated by reference. Regulatory Factor X, 5 (influences HLA class II expression) (RFX5, Accession NM_000449) is another VGAM26 host target gene. RFX5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RFX5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RFX5 BINDING SITE, designated SEQ ID:39, to the nucleotide sequence of VGAM26 RNA, herein designated VGAM RNA, also designated SEQ ID:27.

[0832] Another function of VGAM26 is therefore inhibition of Regulatory Factor X, 5 (influences HLA class II expression) (RFX5, Accession NM_000449), a gene which activates transcription from class II MHC promoters. Accordingly, utilities of VGAM26 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RFX5. The function of RFX5 has been established by previous studies. Major histocompatibility complex (MHC) class II molecules are heterodimeric transmembrane glycoproteins consisting of alpha and beta chains. In man, there are 3 MHC class II isotypes: HLA-DR, -DP, and -DQ. MHC class II molecules play a key role in the immune sys-

tem. They present exogenous antigenic peptides to the receptor of CD4⁺ T-helper lymphocytes, thereby triggering the antigen-specific T-cell activation events required for the initiation and sustenance of immune responses. Durand et al. (1997) noted that the crucial role in the control of the immune response is exemplified by the finding that ectopic or aberrantly high levels of MHC class II expression is associated with autoimmune diseases, while a lack of MHC class II expression results in a severe immunodeficiency syndrome called MHC class II deficiency, or the bare lymphocyte syndrome type II (BLS; 209920). At least 4 complementation groups have been identified in B-cell lines established from patients with BLS. The molecular defect responsible for complementation group A resides in the gene encoding CIITA (MHC2TA; 600005). CIITA is a non-DNA-binding transactivator that functions as a molecular switch controlling both cell-type-specific and inducible MHC class II gene transcription. In contrast, the defects in complementation groups B, C, and D all lead to a deficiency in RFX, a nuclear protein complex that binds to the X box of MHC class II promoters (see OMIM Ref. No. RFX2; 142765). The lack of RFX binding activity in complementation group C results from mutations in the

gene encoding the 75-kD subunit of RFX (Steimle et al., 1995). This gene was called RFX5 because it is the fifth member of the growing family of DNA-binding proteins sharing a novel and highly characteristic DNA-binding domain called the RFX motif. Nekrep et al. (2000) demonstrated a direct interaction between the C terminus of RFXAP (OMIM Ref. No. 601861) and RFXANK (OMIM Ref. No. 603200); mutant RFXAP or RFXANK proteins failed to bind. The authors found that RFX5 binds only to the RFXANK-RFXAP scaffold and not to either protein alone. However, neither the scaffold nor RFX5 alone can bind DNA. Nekrep et al. (2000) concluded that the binding of the RFXANK-RFXAP scaffold to RFX5 leads to a conformational change in the latter that exposes the DNA-binding domain of RFX5. The DNA-binding domain of RFX5 anchors the RFX complex to MHC class II X and S promoter boxes. Another part of the RFX5 protein interacts with MHC2TA. The authors pointed out that mutation of either protein in complementation group B or group D of BLS patients prevents its binding to the other protein, explaining why MHC class II promoters are bare in the bare lymphocyte syndrome.

[0833] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

- [0834] Durand, B.; Sperisen, P.; Emery, P.; Barras, E.; Zufferey, M.; Mach, B.; Reith, W. : RFXAP, a novel subunit of the RFX DNA binding complex is mutated in MHC class II deficiency. EMBO J. 16: 1045–1055, 1997. ; and
- [0835] Nekrep, N.; Jabrane–Ferrat, N.; Peterlin, B. M. : Mutations in the bare lymphocyte syndrome define critical steps in the assembly of the regulatory factor X complex. Molec. Cell Biol. 2.
- [0836] Further studies establishing the function and utilities of RFX5 are found in John Hopkins OMIM database record ID 601863, and in cited publications numbered 21, 266, 441, 268, 440–278, 27 and 627 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. CUB and Sushi Multiple Domains 1 (CSMD1, Accession XM_054838) is another VGAM26 host target gene. CSMD1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CSMD1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CSMD1 BINDING SITE, designated SEQ

ID:301, to the nucleotide sequence of VGAM26 RNA, herein designated VGAM RNA, also designated SEQ ID:27.

[0837] Another function of VGAM26 is therefore inhibition of CUB and Sushi Multiple Domains 1 (CSMD1, Accession XM_054838). Accordingly, utilities of VGAM26 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CSMD1. MGC15438 (Accession NM_032874) is another VGAM26 host target gene.

MGC15438 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC15438, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC15438 BINDING SITE, designated SEQ ID:220, to the nucleotide sequence of VGAM26 RNA, herein designated VGAM RNA, also designated SEQ ID:27.

[0838] Another function of VGAM26 is therefore inhibition of MGC15438 (Accession NM_032874). Accordingly, utilities of VGAM26 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC15438. NYD-SP18 (Accession NM_032599) is another VGAM26 host target gene. NYD-SP18 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by NYD-SP18, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NYD-SP18 BINDING SITE, designated SEQ ID:217, to the nucleotide sequence of VGAM26 RNA, herein designated VGAM RNA, also designated SEQ ID:27.

[0839] Another function of VGAM26 is therefore inhibition of NYD-SP18 (Accession NM_032599). Accordingly, utilities of VGAM26 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NYD-SP18. Olfactomedin 3 (OLFM3, Accession XM_088951) is another VGAM26 host target gene. OLFM3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by OLFM3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OLFM3 BINDING SITE, designated SEQ ID:340, to the nucleotide sequence of VGAM26 RNA, herein designated VGAM RNA, also designated SEQ ID:27.

[0840] Another function of VGAM26 is therefore inhibition of Olfactomedin 3 (OLFM3, Accession XM_088951). Accord-

ingly, utilities of VGAM26 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OLFM3. Ribosomal Protein L13a (RPL13A, Accession NM_012423) is another VGAM26 host target gene. RPL13A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RPL13A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RPL13A BINDING SITE, designated SEQ ID:115, to the nucleotide sequence of VGAM26 RNA, herein designated VGAM RNA, also designated SEQ ID:27.

[0841] Another function of VGAM26 is therefore inhibition of Ribosomal Protein L13a (RPL13A, Accession NM_012423). Accordingly, utilities of VGAM26 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RPL13A. LOC129452 (Accession XM_059359) is another VGAM26 host target gene. LOC129452 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC129452, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nu-

cleotide sequences of LOC129452 BINDING SITE, designated SEQ ID:310, to the nucleotide sequence of VGAM26 RNA, herein designated VGAM RNA, also designated SEQ ID:27.

[0842] Another function of VGAM26 is therefore inhibition of LOC129452 (Accession XM_059359). Accordingly, utilities of VGAM26 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC129452. LOC150197 (Accession XM_086801) is another VGAM26 host target gene. LOC150197 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150197, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150197 BINDING SITE, designated SEQ ID:335, to the nucleotide sequence of VGAM26 RNA, herein designated VGAM RNA, also designated SEQ ID:27.

[0843] Another function of VGAM26 is therefore inhibition of LOC150197 (Accession XM_086801). Accordingly, utilities of VGAM26 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150197. LOC162239 (Accession XM_091439) is an-

other VGAM26 host target gene. LOC162239 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC162239, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC162239 BINDING SITE, designated SEQ ID:344, to the nucleotide sequence of VGAM26 RNA, herein designated VGAM RNA, also designated SEQ ID:27.

[0844] Another function of VGAM26 is therefore inhibition of LOC162239 (Accession XM_091439). Accordingly, utilities of VGAM26 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC162239. LOC219972 (Accession XM_166227) is another VGAM26 host target gene. LOC219972 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219972, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219972 BINDING SITE, designated SEQ ID:379, to the nucleotide sequence of VGAM26 RNA, herein designated VGAM RNA, also designated SEQ ID:27.

[0845] Another function of VGAM26 is therefore inhibition of LOC219972 (Accession XM_166227). Accordingly, utilities of VGAM26 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219972. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 27 (VGAM27) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0846] VGAM27 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM27 was detected is described hereinabove with reference to Figs. 1–8.

[0847] VGAM27 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Immunodeficiency Virus 1. VGAM27 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0848] VGAM27 gene encodes a VGAM27 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM27

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM27 precursor RNA is designated SEQ ID:13, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:13 is located at position 1810 relative to the genome of Human Immunodeficiency Virus 1.

[0849] VGAM27 precursor RNA folds onto itself, forming VGAM27 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0850] An enzyme complex designated DICER COMPLEX, `dices` the VGAM27 folded precursor RNA into VGAM27 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 60%) nucleotide sequence of VGAM27 RNA is designated SEQ ID:28, and is provided hereinbelow with reference to the sequence listing part.

[0851] VGAM27 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM27 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM27 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[0852] VGAM27 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM27 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM27 RNA is an accurate or a partial inverted-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host tar-

get binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM27 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM27 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[0853] The complementary binding of VGAM27 RNA, herein designated VGAM RNA, to host target binding sites on VGAM27 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM27 host target RNA into VGAM27 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0854] It is appreciated that VGAM27 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM27 host target genes. The mRNA of each one of this plurality of VGAM27 host target genes comprises one or more host target binding sites, each

having a nucleotide sequence which is at least partly complementary to VGAM27 RNA, herein designated VGAM RNA, and which when bound by VGAM27 RNA causes inhibition of translation of respective one or more VGAM27 host target proteins.

[0855] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM27 gene, herein designated VGAM GENE, on one or more VGAM27 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[0856] It is yet further appreciated that a function of VGAM27 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM27 include diagnosis, prevention and treatment of viral infection by Human Immunodeficiency Virus 1. Specific functions, and accordingly utilities, of VGAM27 correlate with, and may be deduced from, the identity of the host target genes which VGAM27 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0857] Nucleotide sequences of the VGAM27 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM27 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM27 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM27 are further described hereinbelow with reference to Table 1.

[0858] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM27 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM27 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0859] As mentioned hereinabove with reference to Fig. 1, a

function of VGAM27 gene, herein designated VGAM is inhibition of expression of VGAM27 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM27 correlate with, and may be deduced from, the identity of the target genes which VGAM27 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[0860] DEAD/H (Asp-Glu-Ala-Asp/His) Box Polypeptide 6 (RNA helicase, 54kDa) (DDX6, Accession NM_004397) is a VGAM27 host target gene. DDX6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DDX6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DDX6 BINDING SITE, designated SEQ ID:80, to the nucleotide sequence of VGAM27 RNA, herein designated VGAM RNA, also designated SEQ ID:28.

[0861] A function of VGAM27 is therefore inhibition of DEAD/H (Asp-Glu-Ala-Asp/His) Box Polypeptide 6 (RNA helicase, 54kDa) (DDX6, Accession NM_004397), a gene which is putative RNA helicases. Accordingly, utilities of VGAM27 include diagnosis, prevention and treatment of diseases

and clinical conditions associated with DDX6. The function of DDX6 has been established by previous studies. DEAD box proteins are putative RNA helicases that have a characteristic Asp–Glu–Ala–Asp (DEAD) box as 1 of 8 highly conserved sequence motifs. Akao et al. (1991) cloned the breakpoint of the t(11;14)(q23;q32) in B–cell lymphoma, as represented in the RC–K8 cell line, and named the locus RCK. By pulsed field gel electrophoresis, RCK was shown to be centromeric to the gene for porphobilinogen deaminase (OMIM Ref. No. 176000), while the breakpoints of t(11;19)(q23;p13) were detected by the CD3D gene probe (OMIM Ref. No. 186790), which is centromeric to RCK. Akao et al. (1992) did long–range mapping from the CD3 genes to the PBGD gene on 11q23 to determine the relationship between RCK and MLL–ALL1 (OMIM Ref. No. 159555). They showed that RCK and MLL are on different NotI fragments, indicating that 2 different genes are associated with 11q23 translocations in hematopoietic tumors. Seto et al. (1995) found that the RCK/P54 gene, which had been found to encode a 472 to 483 amino acid–peptide belonging to the RNA helicase/translation initiation factor family, is highly conserved in the mouse. The mouse cDNA showed 93.7% nucleotide identity and 97.7% pre–

dicted amino acid identity with human RCK. Lu and Yunis (1992) cloned a putative human RNA helicase, p54, from a lymphoid cell line with chromosomal breakpoint 11q23.3. The predicted amino acid sequence shared 75% identity with the female germline-specific RNA helicase ME31B gene of *Drosophila*. Unlike ME31B, however, the new gene expressed an abundant transcript in a large number of adult tissues and its 5-prime noncoding region was found to be split in a t(11;14)(q23.3;q32.3) cell line from a diffuse large B-cell lymphoma. Tunnacliffe et al. (1993) assigned the HLR2 gene more precisely using a panel of sequence tagged sites (STSs) representing 30 markers previously assigned to 11q23. Using fluorescence in situ hybridization, Akao and Matsuda (1996) mapped the Ddx6 gene to mouse chromosome 9.

[0862] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0863] Akao, Y.; Seto, M.; Yamamoto, K.; Iida, S.; Nakazawa, S.; Inazawa, J.; Abe, T.; Takahashi, T.; Ueda, R. : The RCK gene associated with t(11;14) translocation is distinct from the MLL/ALL-1 gene with t(4;11) and t(11;19) translocations. *Cancer Res.* 52: 6083–6087, 1992. ; and

[0864] Akao, Y.; Tsujimoto, Y.; Finan, J.; Nowell, P. C.; Croce, C. M. : Molecular characterization of a t(11;14)(q23;q32) chromosome translocation in a B-cell lymphoma. Cancer Res. 50: 4856-4.

[0865] Further studies establishing the function and utilities of DDX6 are found in John Hopkins OMIM database record ID 600326, and in cited publications numbered 397-403 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. LOC126917 (Accession XM_059091) is another VGAM27 host target gene. LOC126917 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC126917, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC126917 BINDING SITE, designated SEQ ID:309, to the nucleotide sequence of VGAM27 RNA, herein designated VGAM RNA, also designated SEQ ID:28.

[0866] Another function of VGAM27 is therefore inhibition of LOC126917 (Accession XM_059091). Accordingly, utilities of VGAM27 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC126917. LOC170395 (Accession XM_084325) is another VGAM27 host target gene. LOC170395 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC170395, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC170395 BINDING SITE, designated SEQ ID:316, to the nucleotide sequence of VGAM27 RNA, herein designated VGAM RNA, also designated SEQ ID:28.

[0867] Another function of VGAM27 is therefore inhibition of LOC170395 (Accession XM_084325). Accordingly, utilities of VGAM27 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC170395. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 28 (VGAM28) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0868] VGAM28 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM28 was detected is described hereinabove with reference to Figs. 1–8.

[0869] VGAM28 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Immunodeficiency Virus 1. VGAM28 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0870] VGAM28 gene encodes a VGAM28 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM28 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM28 precursor RNA is designated SEQ ID:14, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:14 is located at position 728 relative to the genome of Human Immunodeficiency Virus 1.

[0871] VGAM28 precursor RNA folds onto itself, forming VGAM28 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first

half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0872] An enzyme complex designated DICER COMPLEX, `dices` the VGAM28 folded precursor RNA into VGAM28 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 76%) nucleotide sequence of VGAM28 RNA is designated SEQ ID:29, and is provided hereinbelow with reference to the sequence listing part.

[0873] VGAM28 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM28 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM28 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[0874] VGAM28 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM28 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM28 RNA is an accurate or a partial inverted-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM28 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM28 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[0875] The complementary binding of VGAM28 RNA, herein designated VGAM RNA, to host target binding sites on VGAM28 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM28 host target RNA into VGAM28 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0876] It is appreciated that VGAM28 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM28 host target genes. The mRNA of each one of this plurality of VGAM28 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM28 RNA, herein designated VGAM RNA, and which when bound by VGAM28 RNA causes inhibition of translation of respective one or more VGAM28 host target proteins.

[0877] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM28 gene, herein designated VGAM GENE, on one or more VGAM28 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific

complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[0878] It is yet further appreciated that a function of VGAM28 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM28 include diagnosis, prevention and treatment of viral infection by Human Immunodeficiency Virus 1. Specific functions, and accordingly utilities, of VGAM28 correlate with, and may be deduced from, the identity of the host target genes which VGAM28 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0879] Nucleotide sequences of the VGAM28 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM28 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM28 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, of VGAM28 are further described hereinbelow with reference to Table 1.

[0880] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM28 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM28 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0881] As mentioned hereinabove with reference to Fig. 1, a function of VGAM28 gene, herein designated VGAM is inhibition of expression of VGAM28 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM28 correlate with, and may be deduced from, the identity of the target genes which VGAM28 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[0882] ATP-binding Cassette, Sub-family C (CFTR/MRP), Member 3 (ABCC3, Accession NM_020038) is a VGAM28 host target gene. ABCC3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ABCC3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of ABCC3 BINDING SITE, designated SEQ ID:170, to the nucleotide sequence of VGAM28 RNA, herein designated VGAM RNA, also designated SEQ ID:29.

[0883] A function of VGAM28 is therefore inhibition of ATP-binding Cassette, Sub-family C (CFTR/MRP), Member 3 (ABCC3, Accession NM_020038), a gene which may act as an inducible transporter in the biliary and intestinal excretion of organic anions. Accordingly, utilities of VGAM28 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ABCC3. The function of ABCC3 has been established by previous studies. Bile secretion in liver is driven in large part by ATP-binding cassette (ABC)-type proteins that reside in the canalicular membrane and effect ATP-dependent transport of bile acids, phospholipids, and non-bile acid organic anions. Canalicular ABC-type proteins can be classified into 2 subfamilies based on membrane topology and sequence identity: MDR1 (multidrug resistance-1; 171050), MDR3 (multidrug resistance-3; 171060), and SPGP (bile salt export pump, or sister of P-glycoprotein; 603201) resemble the multidrug resistance P-glycoprotein, whereas MRP2 (OMIM Ref. No. 601107) is

similar in structure and sequence to the multidrug resistance protein MRP1 (OMIM Ref. No. 158343) and transports similar substrates. Kool et al. (1999) detected expression of ABCC3 in the lateral side of cholangiocytes and in the basolateral membranes of hepatocytes, where it mediates transport of S-glutathione. When expressed in ovarian carcinoma cells, ABCC3 conferred resistance to the anticancer drugs methotrexate, etoposide, and teniposide. The authors noted that sequence analysis of ABCC3 predicts a protein organized in a way similar to ABCC1 and ABCC2. Using FISH, Uchiumi et al. (1998) mapped the ABCC3 gene to 17q22.

[0884] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0885] Kool, M.; van der Linden, M.; de Haas, M.; Scheffer, G. L.; de Vree, J. M. L.; Smith, A. J.; Jansen, G.; Peters, G. J.; Ponne, N.; Scheper, R. J.; Oude Elferink, R. P. J.; Baas, F.; Borst, P. : MRP3, an organic anion transporter able to transport anti-cancer drugs. Proc. Nat. Acad. Sci. 96: 6914-6919, 1999. ; and

[0886] Uchiumi, T.; Hinoshita, E.; Haga, S.; Nakamura, T.; Tanaka, T.; Toh, S.; Furukawa, M.; Kawabe, T.; Wada, M.; Kagotani,

K.; Okumura, K.; Kohno, K.; Akiyama, S.; Kuwano, M. : Isolation of.

- [0887] Further studies establishing the function and utilities of ABCC3 are found in John Hopkins OMIM database record ID 604323, and in cited publications numbered 213–21 and 389 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Caspase 3, Apoptosis–related Cysteine Protease (CASP3, Accession NM_032991) is another VGAM28 host target gene. CASP3 BINDING SITE1 and CASP3 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by CASP3, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CASP3 BINDING SITE1 and CASP3 BINDING SITE2, designated SEQ ID:225 and SEQ ID:79 respectively, to the nucleotide sequence of VGAM28 RNA, herein designated VGAM RNA, also designated SEQ ID:29.
- [0888] Another function of VGAM28 is therefore inhibition of Caspase 3, Apoptosis–related Cysteine Protease (CASP3, Accession NM_032991), a gene which is one apoptosis–related cysteine protease and is important for the initiation of apoptotic cell death. Accordingly, utilities of VGAM28

include diagnosis, prevention and treatment of diseases and clinical conditions associated with CASP3. The function of CASP3 has been established by previous studies. Nicholson et al. (1995) developed a potent peptide aldehyde inhibitor and showed that it prevents apoptotic events in vitro, suggesting that apopain/CPP32 is important for the initiation of apoptotic cell death. Apoptosis of human endothelial cells after growth factor deprivation is associated with rapid and dramatic upregulation of cyclin A-associated cyclin-dependent kinase-2 (CDK2; 116953) activity. Levkau et al. (1998) showed that in apoptotic cells the carboxyl termini of the CDK inhibitors CDKN1A (OMIM Ref. No. 116899) and CDKN1B (OMIM Ref. No. 600778) are truncated by specific cleavage. The enzyme involved in this cleavage is CASP3 and/or a CASP3-like caspase. After cleavage, CDKN1A loses its nuclear localization sequence and exits the nucleus. Cleavage of CDKN1A and CDKN1B resulted in a substantial reduction in their association with nuclear cyclin-CDK2 complexes, leading to a dramatic induction of CDK2 activity. Dominant-negative CDK2, as well as a mutant CDKN1A resistant to caspase cleavage, partially suppressed apoptosis. These data suggested that CDK2 activation, through caspase-mediated cleavage of

CDK inhibitors, may be instrumental in the execution of apoptosis following caspase activation. Animal model experiments lend further support to the function of CASP3. To analyze the function of CPP32 in vivo, Kuida et al. (1996) generated CPP32-deficient mice by homologous recombination. These mice, born at a frequency lower than expected by mendelian genetics, were smaller than their littermates and died at 1 to 3 weeks of age. Although their thymocytes retained normal susceptibility to various apoptotic stimuli, brain development in CPP32-deficient mice was profoundly affected, and discernible by embryonic day 12, resulting in a variety of hypoplasias and disorganized cell deployment. These supernumerary cells were postmitotic and terminally differentiated by the postnatal stage. Pyknotic clusters at sites of major morphogenetic change during normal brain development were not observed in the mutant embryos, indicating increased apoptosis in the absence of CPP32. Thus, CPP32 was shown by Kuida et al. (1996) to play a critical role during morphogenetic cell death in the mammalian brain.

[0889] It is appreciated that the abovementioned animal model for CASP3 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appre-

ciated from the publications sited hereinbelow.

- [0890] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:
- [0891] Kuida, K.; Zheng, T. S.; Na, S.; Kuan, C.; Yang, D.; Kara-suyama, H.; Rakio, P.; Flavell, R. A. : Decreased apoptosis in the brain and premature lethality in CPP32-deficient mice. *Nature* 384: 368–372, 1996. ; and
- [0892] Nicholson, D. W.; Ali, A.; Thornberry, N. A.; Vaillancourt, J. P.; Ding, C. K.; Gallant, M.; Gareau, Y.; Griffin, P. R.; La-belle, M.; Lazebnik, Y. A.; Munday, N. A.; Raju, S. M.; Smulso.
- [0893] Further studies establishing the function and utilities of CASP3 are found in John Hopkins OMIM database record ID 600636, and in sited publications numbered 315–317, 52, 318–320, 12, 32 and 324–323 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Ems1 Sequence (mammary tumor and squamous cell carcinoma-associated (p80/85 src substrate) (EMS1, Accession NM_138565) is another VGAM28 host target gene. EMS1 BINDING SITE1 and EMS1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by EMS1, corresponding

to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EMS1 BINDING SITE1 and EMS1 BINDING SITE2, designated SEQ ID:240 and SEQ ID:97 respectively, to the nucleotide sequence of VGAM28 RNA, herein designated VGAM RNA, also designated SEQ ID:29.

[0894] Another function of VGAM28 is therefore inhibition of Ems1 Sequence (mammary tumor and squamous cell carcinoma-associated (p80/85 src substrate) (EMS1, Accession NM_138565), a gene which may contribute to the organization of cell structure. in transformed cells may contribute to cellular growth regulation and transformation. Accordingly, utilities of VGAM28 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EMS1. The function of EMS1 has been established by previous studies. Amplification of the 11q13 region is frequently found in breast cancer and in squamous cell carcinomas of the head and neck. The known oncogenes within the amplified 11q13 region, INT2 (OMIM Ref. No. 164950) and FGF4 (OMIM Ref. No. 164980), are rarely expressed in these tumors, indicating that another, hitherto unidentified gene or genes are involved in the

unfavorable clinical course of disease associated with such amplification. To identify the gene or genes, Schuuring et al. (1992) constructed a cDNA library from a cell line with an 11q13 amplification and performed a differential cDNA cloning using labeled cDNAs from human squamous cell carcinoma cell lines with and without an 11q13 amplification. They isolated 2 cDNA clones, U21B31 and U21C8, which recognized genes amplified and overexpressed in cell lines harboring an 11q13 amplification. Sequence analysis of the U21C8 cDNA clone revealed no homology to known genes; they called this gene EMS1. The U21B31 cDNA clone corresponded to the 3-prime end of the PRAD1 protooncogene (OMIM Ref. No. 168461). Van Damme et al. (1997) stated that EMS1 is the human homolog of cortactin, an actin-binding protein involved in the restructuring of the cortical actin cytoskeleton. Cortactin is a substrate for the pp60v-src tyrosine kinase (see OMIM Ref. No. 190090). Cortactin is overexpressed in carcinoma cells with an amplification of 11q13 and is found in 2 forms, designated p80 and p85. Van Damme et al. (1997) found that in carcinoma cells with the 11q13 amplification, p85 was produced from p80 by posttranslational modification. Also, treatment of these cells with

epidermal growth factor (OMIM Ref. No. 131530) or vanadate caused conversion of p80 to p85 and enhanced phosphorylation of the p85 form. Both overexpression and posttranslational modification of cortactin coincided with its redistribution from the cytoplasm to cell-matrix contact sites, implying a role for cortactin in the modulation of cellular adhesive properties.

[0895] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0896] Schuuring, E.; Verhoeven, E.; Mooi, W. J.; Michalides, R. J. A. M. : Identification and cloning of two overexpressed genes, U21B31/PRAD1 and EMS1, within the amplified chromosome 11q13 region in human carcinomas. *Oncogene* 7: 355–361, 1992. ; and

[0897] van Damme, H.; Brok, H.; Schuuring-Scholtes, E.; Schuuring, E. : The redistribution of cortactin into cell-matrix contact sites in human carcinoma cells with 11q13 amplification is asso.

[0898] Further studies establishing the function and utilities of EMS1 are found in John Hopkins OMIM database record ID 164765, and in cited publications numbered 231–232 listed in the bibliography section hereinbelow, which are

also hereby incorporated by reference. Tumor Necrosis Factor (ligand) Superfamily, Member 6 (TNFSF6, Accession NM_000639) is another VGAM28 host target gene. TNFSF6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TNFSF6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TNFSF6 BINDING SITE, designated SEQ ID:42, to the nucleotide sequence of VGAM28 RNA, herein designated VGAM RNA, also designated SEQ ID:29.

[0899] Another function of VGAM28 is therefore inhibition of Tumor Necrosis Factor (ligand) Superfamily, Member 6 (TNFSF6, Accession NM_000639). Accordingly, utilities of VGAM28 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TNFSF6. Ubiquitin B (UBB, Accession NM_018955) is another VGAM28 host target gene. UBB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UBB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UBB BINDING SITE, design-

nated SEQ ID:166, to the nucleotide sequence of VGAM28 RNA, herein designated VGAM RNA, also designated SEQ ID:29.

[0900] Another function of VGAM28 is therefore inhibition of Ubiquitin B (UBB, Accession NM_018955), a gene which marks cellular proteins for degradation. Accordingly, utilities of VGAM28 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBB. The function of UBB has been established by previous studies. Ubiquitin (see OMIM Ref. No. 191320) may be evolution's most conserved protein, presumably because of its role in several important cellular processes. By in situ hybridization, Webb et al. (1990) assigned the 3-coding unit polyubiquitin gene UBB and its nonprocessed pseudogene to 17p12-p11.1. See also ubiquitin C (OMIM Ref. No. 191340). The protein deposits in neurofibrillary tangles, neuritic plaques, and neuropil threads in the cerebral cortex of patients with Alzheimer disease (AD; 104300) and Down syndrome (OMIM Ref. No. 190685) contain forms of beta-amyloid precursor protein (APP; 104760) and ubiquitin-B that are aberrant in the C terminus. These proteins are not found in young control subjects, whereas the presence of anomalous UBB in el-

derly control patients may indicate early stages of neurodegeneration. The 2 species of aberrant proteins were found by van Leeuwen et al. (1998) to display cellular colocalization, suggesting a common origin, operating at the transcriptional level or by posttranscriptional editing of RNA. This type of transcript mutation is likely an important factor in the widely occurring nonfamilial early- and late-onset forms of AD. The aberrant proteins were not found in patients with Parkinson disease (OMIM Ref. No. 168600). Using 2 different sensitive approaches, van Leeuwen et al. (1998) failed to find any indication of the mutation at the genomic level. The finding that frameshift mutations occur in multiple proteins within the same neuron suggested that a common denominator in the transcription-propagating events was involved. The mechanism of transcript mutation, which was a dinucleotide deletion (delta-GA, delta-GT, or delta-CT), was unclear. The frequently mutated motif in exon 9 of the APP gene, GAGAGAGA, is an extended version of the GAGAG in the vasopressin gene (OMIM Ref. No. 192340), which shows a GA deletion in vasopressin transcripts of the homozygous Brattleboro rats with diabetes insipidus. The authors commented that transcript mutations may be a widely occur-

ring phenomenon. In principle, each transcript containing a susceptible motif, such as GAGAG, could undergo such a process. Van Leeuwen et al. (1998) stated that the process is probably not limited to postmitotic cells; however, postmitotic neurons are less capable of compensating for transcript-modifying activity and are thus particularly sensitive to the accumulation of frameshifted proteins. Thus, during aging, single neurons may generate and accumulate abnormal proteins, consequently leading to cellular disturbances and causing degeneration. The mechanism of dinucleotide deletion at the transcript level may well underlie a number of neurodegenerative pathologies

[0901] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0902] van Leeuwen, F. W.; de Kleijn, D. P. V.; van den Hurk, H. H.; Neubauer, A.; Sonnemans, M. A. F.; Sluijs, J. A.; Koycu, S.; Ramdjielal, R. D. J.; Salehi, A.; Martens, G. J. M.; Grosveld, F. G.; Burbach, J. P. H.; Hol, E. M. : Frameshift mutants of beta-amyloid precursor protein and ubiquitin-B in Alzheimer's and Down patients. Science 279: 242-247, 1998. ; and

[0903] Webb, G. C.; Baker, R. T.; Fagan, K.; Board, P. G. : Local-

ization of the human UbB polyubiquitin gene to chromosome band 17p11.1–17p12. Am. J. Hum. Genet. 46: 308–315, 1990.

[0904] Further studies establishing the function and utilities of UBB are found in John Hopkins OMIM database record ID 191339, and in cited publications numbered 624 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. A Kinase (PRKA) Anchor Protein 10 (AKAP10, Accession NM_007202) is another VGAM28 host target gene. AKAP10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AKAP10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AKAP10 BINDING SITE, designated SEQ ID:113, to the nucleotide sequence of VGAM28 RNA, herein designated VGAM RNA, also designated SEQ ID:29.

[0905] Another function of VGAM28 is therefore inhibition of A Kinase (PRKA) Anchor Protein 10 (AKAP10, Accession NM_007202). Accordingly, utilities of VGAM28 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AKAP10. 2,4-dienoyl CoA Re-

ductase 2, Peroxisomal (DECR2, Accession NM_020664) is another VGAM28 host target gene. DECR2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DECR2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DECR2 BINDING SITE, designated SEQ ID:176, to the nucleotide sequence of VGAM28 RNA, herein designated VGAM RNA, also designated SEQ ID:29.

[0906] Another function of VGAM28 is therefore inhibition of 2,4-dienoyl CoA Reductase 2, Peroxisomal (DECR2, Accession NM_020664). Accordingly, utilities of VGAM28 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DECR2. KIAA0240 (Accession XM_166479) is another VGAM28 host target gene. KIAA0240 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0240, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0240 BINDING SITE, designated SEQ ID:383, to the nucleotide sequence of VGAM28 RNA,

herein designated VGAM RNA, also designated SEQ ID:29.

[0907] Another function of VGAM28 is therefore inhibition of KIAA0240 (Accession XM_166479). Accordingly, utilities of VGAM28 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0240. MGC16385 (Accession NM_145039) is another VGAM28 host target gene. MGC16385 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by MGC16385, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC16385 BINDING SITE, designated SEQ ID:255, to the nucleotide sequence of VGAM28 RNA, herein designated VGAM RNA, also designated SEQ ID:29.

[0908] Another function of VGAM28 is therefore inhibition of MGC16385 (Accession NM_145039). Accordingly, utilities of VGAM28 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC16385. MGC5139 (Accession XM_058587) is another VGAM28 host target gene. MGC5139 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by MGC5139, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC5139 BINDING SITE, designated SEQ ID:305, to the nucleotide sequence of VGAM28 RNA, herein designated VGAM RNA, also designated SEQ ID:29.

[0909] Another function of VGAM28 is therefore inhibition of MGC5139 (Accession XM_058587). Accordingly, utilities of VGAM28 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC5139. P5-1 (Accession NM_006674) is another VGAM28 host target gene. P5-1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by P5-1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of P5-1 BINDING SITE, designated SEQ ID:110, to the nucleotide sequence of VGAM28 RNA, herein designated VGAM RNA, also designated SEQ ID:29.

[0910] Another function of VGAM28 is therefore inhibition of P5-1 (Accession NM_006674). Accordingly, utilities of VGAM28 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with P5-1. TED (Accession NM_015686) is another VGAM28 host target gene. TED BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TED, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TED BINDING SITE, designated SEQ ID:143, to the nucleotide sequence of VGAM28 RNA, herein designated VGAM RNA, also designated SEQ ID:29.

[0911] Another function of VGAM28 is therefore inhibition of TED (Accession NM_015686). Accordingly, utilities of VGAM28 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TED. LOC133418 (Accession XM_059649) is another VGAM28 host target gene. LOC133418 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC133418, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC133418 BINDING SITE, designated SEQ ID:311, to the nucleotide sequence of VGAM28 RNA, herein designated VGAM RNA, also designated SEQ

ID:29.

[0912] Another function of VGAM28 is therefore inhibition of LOC133418 (Accession XM_059649). Accordingly, utilities of VGAM28 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC133418. LOC152402 (Accession XM_098222) is another VGAM28 host target gene. LOC152402 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152402, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152402 BINDING SITE, designated SEQ ID:353, to the nucleotide sequence of VGAM28 RNA, herein designated VGAM RNA, also designated SEQ ID:29.

[0913] Another function of VGAM28 is therefore inhibition of LOC152402 (Accession XM_098222). Accordingly, utilities of VGAM28 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152402. LOC158677 (Accession XM_098976) is another VGAM28 host target gene. LOC158677 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC158677, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158677 BINDING SITE, designated SEQ ID:360, to the nucleotide sequence of VGAM28 RNA, herein designated VGAM RNA, also designated SEQ ID:29.

[0914] Another function of VGAM28 is therefore inhibition of LOC158677 (Accession XM_098976). Accordingly, utilities of VGAM28 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158677. LOC221715 (Accession XM_168092) is another VGAM28 host target gene. LOC221715 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221715, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221715 BINDING SITE, designated SEQ ID:390, to the nucleotide sequence of VGAM28 RNA, herein designated VGAM RNA, also designated SEQ ID:29.

[0915] Another function of VGAM28 is therefore inhibition of LOC221715 (Accession XM_168092). Accordingly, utilities of VGAM28 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC221715. LOC254746 (Accession XM_170833) is another VGAM28 host target gene. LOC254746 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254746, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254746 BINDING SITE, designated SEQ ID:394, to the nucleotide sequence of VGAM28 RNA, herein designated VGAM RNA, also designated SEQ ID:29.

[0916] Another function of VGAM28 is therefore inhibition of LOC254746 (Accession XM_170833). Accordingly, utilities of VGAM28 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254746. LOC255098 (Accession XM_170912) is another VGAM28 host target gene. LOC255098 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC255098, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255098 BINDING SITE, designated SEQ ID:396, to

the nucleotide sequence of VGAM28 RNA, herein designated VGAM RNA, also designated SEQ ID:29.

[0917] Another function of VGAM28 is therefore inhibition of LOC255098 (Accession XM_170912). Accordingly, utilities of VGAM28 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255098. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 29 (VGAM29) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0918] VGAM29 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM29 was detected is described hereinabove with reference to Figs. 1–8.

[0919] VGAM29 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Immunodeficiency Virus 1. VGAM29 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0920] VGAM29 gene encodes a VGAM29 precursor RNA, herein

designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM29 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM29 precursor RNA is designated SEQ ID:15, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:15 is located at position 5471 relative to the genome of Human Immunodeficiency Virus 1.

[0921] VGAM29 precursor RNA folds onto itself, forming VGAM29 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0922] An enzyme complex designated DICER COMPLEX, `dices` the VGAM29 folded precursor RNA into VGAM29 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 70%) nucleotide sequence of VGAM29 RNA is designated SEQ ID:30, and is provided hereinbelow with reference to the sequence listing part.

[0923] VGAM29 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM29 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM29 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[0924] VGAM29 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM29 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM29 RNA is an accurate or a partial inverted-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, desig-

nated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM29 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM29 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[0925] The complementary binding of VGAM29 RNA, herein designated VGAM RNA, to host target binding sites on VGAM29 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM29 host target RNA into VGAM29 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0926] It is appreciated that VGAM29 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM29 host target genes. The mRNA of

each one of this plurality of VGAM29 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM29 RNA, herein designated VGAM RNA, and which when bound by VGAM29 RNA causes inhibition of translation of respective one or more VGAM29 host target proteins.

[0927] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM29 gene, herein designated VGAM GENE, on one or more VGAM29 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[0928] It is yet further appreciated that a function of VGAM29 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM29 include diagnosis, prevention and treatment of viral infection by Human Immunodeficiency Virus 1. Specific functions, and accordingly utilities, of VGAM29 correlate with, and may be deduced from, the identity of the host target genes which VGAM29 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0929] Nucleotide sequences of the VGAM29 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM29 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM29 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM29 are further described hereinbelow with reference to Table 1.

[0930] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM29 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM29 RNA, herein designated VGAM RNA, are described hereinbelow with refer-

ence to Table 2.

[0931] As mentioned hereinabove with reference to Fig. 1, a function of VGAM29 gene, herein designated VGAM is inhibition of expression of VGAM29 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM29 correlate with, and may be deduced from, the identity of the target genes which VGAM29 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[0932] A Disintegrin and Metalloproteinase Domain 19 (meltrin beta) (ADAM19, Accession NM_033274) is a VGAM29 host target gene. ADAM19 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADAM19, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADAM19 BINDING SITE, designated SEQ ID:228, to the nucleotide sequence of VGAM29 RNA, herein designated VGAM RNA, also designated SEQ ID:30.

[0933] A function of VGAM29 is therefore inhibition of A Disintegrin and Metalloproteinase Domain 19 (meltrin beta) (ADAM19, Accession NM_033274), a gene which partici-

pates in the proteolytic processing of beta-type neuregulin isoforms . Accordingly, utilities of VGAM29 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADAM19. The function of ADAM19 has been established by previous studies. Members of the ADAM family are cell surface proteins containing a disintegrin cell adhesion domain and a metalloproteinase domain. Inoue et al. (1998) cloned full-length cDNAs of mouse Adam19, which they referred to as meltrin-beta (see OMIM Ref. No. ADAM12, 602714). The ADAM19 gene encodes a 920-amino acid polypeptide, and Inoue et al. (1998) found that its sequence was most similar to ADAM12 and ADAM13. Northern blot analysis revealed that a major 6.5-kb transcript was expressed in all mouse tissues tested. Hirohata et al. (1998) used radiation hybrids to map ADAM19 to mouse chromosome 11 and to human chromosome 5q32-q33.

[0934] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[0935] Hirohata, S.; Seldin, M. F.; Apte, S. S. : Chromosomal assignment of two ADAM genes, TACE (ADAM17) and MLTNB (ADAM19), to human chromosomes 2 and 5, re-

spectively, and of Mltnb to mouse chromosome 11. Genomics 54: 178–179, 1998. ; and

[0936] Inoue, D.; Reid, M.; Lum, L.; Kratzschmar, J.; Weskamp, G.; Myung, Y. M.; Baron, R.; Blobel, C. P. : Cloning and initial characterization of mouse meltrin beta and analysis of the expe.

[0937] Further studies establishing the function and utilities of ADAM19 are found in John Hopkins OMIM database record ID 603640, and in cited publications numbered 433–434 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. LFG (Accession XM_084780) is another VGAM29 host target gene. LFG BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LFG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LFG BINDING SITE, designated SEQ ID:319, to the nucleotide sequence of VGAM29 RNA, herein designated VGAM RNA, also designated SEQ ID:30.

[0938] Another function of VGAM29 is therefore inhibition of LFG (Accession XM_084780). Accordingly, utilities of VGAM29 include diagnosis, prevention and treatment of diseases

and clinical conditions associated with LFG. Nucleolar Protein Family A, Member 2 (H/ACA small nucleolar RNPs) (NOLA2, Accession XM_170506) is another VGAM29 host target gene. NOLA2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by NOLA2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NOLA2 BINDING SITE, designated SEQ ID:393, to the nucleotide sequence of VGAM29 RNA, herein designated VGAM RNA, also designated SEQ ID:30.

[0939] Another function of VGAM29 is therefore inhibition of Nucleolar Protein Family A, Member 2 (H/ACA small nucleolar RNPs) (NOLA2, Accession XM_170506), a gene which may play a role in ribosomal RNA pseudouridylation. Accordingly, utilities of VGAM29 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NOLA2. The function of NOLA2 has been established by previous studies. Small nucleolar RNAs (snoRNAs) of the H/ACA class specify the sites of uridine-to-pseudouridine conversion. The H and ACA motifs are located in the hinge and tail, respectively, of a 2-domain hairpin-hinge-hairpin-tail structure. The uridine conver-

sion process, together with the removal of the spacer region and the 2-prime-O-methylation of ribose groups, which is carried out by snoRNAs of the C/D class, is required for the generation of functional rRNAs. See Tollervey and Kiss (1997) for further information. By searching an EST database for orthologs of yeast Nhp2, followed by 5-prime and 3-prime RACE, Pogacic et al. (2000) obtained a cDNA encoding NOLA2, which they called NHP2. The deduced 153-amino acid protein is 55% identical to the yeast protein. Complementation analysis showed that the recombinant human protein can replace the yeast protein. Immunoprecipitation and Western blot analysis indicated that NOLA2 associates with NOP10 (NOLA3; 606471), dyskerin (DKC1; 300126), and GAR1 (NOLA1; 606468) in structures corresponding to H/ACA snoRNPs, but not to C/D snoRNPs, and to telomerase. Immunofluorescence microscopy demonstrated colocalization of NOLA2 with NOLA1, NOLA3, and DKC1, but not with fibrillarin (FBL; 134795), in nucleolar dense fibrillar components and in Cajal bodies (also OMIM Ref. No. 600272). Pogacic et al. (2000) concluded that NOLA2 is likely to be a primary RNA-binding protein.

[0940] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

[0941] Pogacic, V.; Dragon, F.; Filipowicz, W. : Human H/ACA small nucleolar RNPs and telomerase share evolutionarily conserved proteins NHP2 and NOP10. *Molec. Cell. Biol.* 20: 9028–9040, 2000. ; and

[0942] Tollervey, D.; Kiss, T. : Function and synthesis of small nucleolar RNAs. *Curr. Opin. Cell Biol.* 9: 337–342, 1997.

[0943] Further studies establishing the function and utilities of NOLA2 are found in John Hopkins OMIM database record ID 606470, and in cited publications numbered 208 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. FLJ10751 (Accession NM_018205) is another VGAM29 host target gene.

FLJ10751 BINDING SITE1 and FLJ10751 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by FLJ10751, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10751 BINDING SITE1 and FLJ10751 BINDING SITE2, designated SEQ ID:158 and SEQ ID:159 respectively, to the nucleotide sequence of VGAM29 RNA, herein designated VGAM RNA,

also designated SEQ ID:30.

[0944] Another function of VGAM29 is therefore inhibition of FLJ10751 (Accession NM_018205). Accordingly, utilities of VGAM29 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10751. KIAA1118 (Accession XM_045581) is another VGAM29 host target gene. KIAA1118 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1118, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1118 BINDING SITE, designated SEQ ID:289, to the nucleotide sequence of VGAM29 RNA, herein designated VGAM RNA, also designated SEQ ID:30.

[0945] Another function of VGAM29 is therefore inhibition of KIAA1118 (Accession XM_045581). Accordingly, utilities of VGAM29 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1118. KIAA1649 (Accession NM_032311) is another VGAM29 host target gene. KIAA1649 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1649, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1649 BINDING SITE, designated SEQ ID:215, to the nucleotide sequence of VGAM29 RNA, herein designated VGAM RNA, also designated SEQ ID:30.

[0946] Another function of VGAM29 is therefore inhibition of KIAA1649 (Accession NM_032311). Accordingly, utilities of VGAM29 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1649. LIMR (Accession NM_018113) is another VGAM29 host target gene. LIMR BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LIMR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LIMR BINDING SITE, designated SEQ ID:157, to the nucleotide sequence of VGAM29 RNA, herein designated VGAM RNA, also designated SEQ ID:30.

[0947] Another function of VGAM29 is therefore inhibition of LIMR (Accession NM_018113). Accordingly, utilities of VGAM29 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with LIMR. MGC14161 (Accession NM_032892) is another VGAM29 host target gene. MGC14161 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC14161, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC14161 BINDING SITE, designated SEQ ID:221, to the nucleotide sequence of VGAM29 RNA, herein designated VGAM RNA, also designated SEQ ID:30.

[0948] Another function of VGAM29 is therefore inhibition of MGC14161 (Accession NM_032892). Accordingly, utilities of VGAM29 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC14161. NJMU-R1 (Accession NM_022344) is another VGAM29 host target gene. NJMU-R1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NJMU-R1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NJMU-R1 BINDING SITE, designated SEQ ID:188, to the nucleotide sequence

of VGAM29 RNA, herein designated VGAM RNA, also designated SEQ ID:30.

[0949] Another function of VGAM29 is therefore inhibition of NJMU-R1 (Accession NM_022344). Accordingly, utilities of VGAM29 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NJMU-R1. Sema Domain, Immunoglobulin Domain (Ig), Short Basic Domain, Secreted, (semaphorin) 3E (SEMA3E, Accession NM_012431) is another VGAM29 host target gene.

SEMA3E BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SEMA3E, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEMA3E BINDING SITE, designated SEQ ID:119, to the nucleotide sequence of VGAM29 RNA, herein designated VGAM RNA, also designated SEQ ID:30.

[0950] Another function of VGAM29 is therefore inhibition of Sema Domain, Immunoglobulin Domain (Ig), Short Basic Domain, Secreted, (semaphorin) 3E (SEMA3E, Accession NM_012431). Accordingly, utilities of VGAM29 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SEMA3E. YKT6 (Accession

NM_006555) is another VGAM29 host target gene. YKT6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by YKT6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of YKT6 BINDING SITE, designated SEQ ID:106, to the nucleotide sequence of VGAM29 RNA, herein designated VGAM RNA, also designated SEQ ID:30.

[0951] Another function of VGAM29 is therefore inhibition of YKT6 (Accession NM_006555). Accordingly, utilities of VGAM29 include diagnosis, prevention and treatment of diseases and clinical conditions associated with YKT6. LOC142972 (Accession XM_036593) is another VGAM29 host target gene. LOC142972 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC142972, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC142972 BINDING SITE, designated SEQ ID:271, to the nucleotide sequence of VGAM29 RNA, herein designated VGAM RNA, also designated SEQ ID:30.

[0952] Another function of VGAM29 is therefore inhibition of LOC142972 (Accession XM_036593). Accordingly, utilities of VGAM29 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC142972. LOC143689 (Accession XM_084609) is another VGAM29 host target gene. LOC143689 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC143689, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC143689 BINDING SITE, designated SEQ ID:318, to the nucleotide sequence of VGAM29 RNA, herein designated VGAM RNA, also designated SEQ ID:30.

[0953] Another function of VGAM29 is therefore inhibition of LOC143689 (Accession XM_084609). Accordingly, utilities of VGAM29 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC143689. LOC148930 (Accession XM_086369) is another VGAM29 host target gene. LOC148930 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC148930, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148930 BINDING SITE, designated SEQ ID:332, to the nucleotide sequence of VGAM29 RNA, herein designated VGAM RNA, also designated SEQ ID:30.

[0954] Another function of VGAM29 is therefore inhibition of LOC148930 (Accession XM_086369). Accordingly, utilities of VGAM29 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148930. LOC220469 (Accession XM_084334) is another VGAM29 host target gene. LOC220469 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC220469, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220469 BINDING SITE, designated SEQ ID:317, to the nucleotide sequence of VGAM29 RNA, herein designated VGAM RNA, also designated SEQ ID:30.

[0955] Another function of VGAM29 is therefore inhibition of LOC220469 (Accession XM_084334). Accordingly, utilities of VGAM29 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC220469. LOC253782 (Accession XM_171023) is another VGAM29 host target gene. LOC253782 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253782, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253782 BINDING SITE, designated SEQ ID:398, to the nucleotide sequence of VGAM29 RNA, herein designated VGAM RNA, also designated SEQ ID:30.

[0956] Another function of VGAM29 is therefore inhibition of LOC253782 (Accession XM_171023). Accordingly, utilities of VGAM29 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253782. LOC92078 (Accession XM_042684) is another VGAM29 host target gene. LOC92078 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC92078, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92078 BINDING SITE, designated SEQ ID:282, to the nucleotide sequence of VGAM29 RNA, herein designated

VGAM RNA, also designated SEQ ID:30.

[0957] Another function of VGAM29 is therefore inhibition of LOC92078 (Accession XM_042684). Accordingly, utilities of VGAM29 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92078. Fig. 9 further provides a conceptual description of novel bioinformatically detected regulatory viral gene, referred to here as Viral Genomic Record 30(VGR30) viral gene, which encodes an `operon-like` cluster of novel viral micro RNA-like genes, each of which in turn modulates expression of at least one host target gene, the function and utility of which at least one host target gene is known in the art.

[0958] VGR30 gene, herein designated VGR GENE, is a novel bioinformatically detected regulatory, non protein coding, RNA viral gene. The method by which VGR30 gene was detected is described hereinabove with reference to Figs. 1-9.

[0959] VGR30 gene encodes VGR30 precursor RNA, herein designated VGR PRECURSOR RNA, an RNA molecule, typically several hundred nucleotides long.

[0960] VGR30 precursor RNA folds spatially, forming VGR30 folded precursor RNA, herein designated VGR FOLDED

PRECURSOR RNA. It is appreciated that VGR30 folded precursor RNA comprises a plurality of what is known in the art as `hairpin` structures. These `hairpin` structures are due to the fact that the nucleotide sequence of VGR30 precursor RNA comprises a plurality of segments, the first half of each such segment having a nucleotide sequence which is at least a partial inversed-reversed sequence of the second half thereof, as is well known in the art.

[0961] VGR30 folded precursor RNA is naturally processed by cellular enzymatic activity into at least 8 separate VGAM precursor RNAs, VGAM15 precursor RNA, VGAM16 precursor RNA, VGAM17 precursor RNA, VGAM18 precursor RNA, VGAM19 precursor RNA, VGAM20 precursor RNA, VGAM21 precursor RNA and VGAM22 precursor RNA, herein schematically represented by VGAM1 FOLDED PRECURSOR through VGAM3 FOLDED PRECURSOR, each of which VGAM precursor RNAs being a hairpin shaped RNA segment, corresponding to VGAM FOLDED PRECURSOR RNA of Fig. 1.

[0962] The above mentioned VGAM precursor RNAs are `diced` by DICER COMPLEX of Fig. 1, yielding respective short RNA segments of about 22 nucleotides in length, VGAM15 RNA, VGAM16 RNA, VGAM17 RNA, VGAM18 RNA, VGAM19

RNA, VGAM20 RNA, VGAM21 RNA and VGAM22 RNA, herein schematically represented by VGAM1 RNA through VGAM3 RNA, each of which VGAM RNAs corresponding to VGAM RNA of Fig. 1.

[0963] VGAM15 RNA, herein schematically represented by VGAM1 RNA through VGAM3 RNA, binds complementarily to a host target binding site located in an untranslated region of VGAM15 host target RNA, herein schematically represented by VGAM1 HOST TARGET RNA through VGAM3 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM15 host target RNA into VGAM15 host target protein, herein schematically represented by VGAM1 HOST TARGET PROTEIN through VGAM3 HOST TARGET PROTEIN, all of Fig. 1.

[0964] VGAM16 RNA, herein schematically represented by VGAM1 RNA through VGAM3 RNA, binds complementarily to a host target binding site located in an untranslated region of VGAM16 host target RNA, herein schematically represented by VGAM1 HOST TARGET RNA through VGAM3 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING

SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM16 host target RNA into VGAM16 host target protein, herein schematically represented by VGAM1 HOST TARGET PROTEIN through VGAM3 HOST TARGET PROTEIN, all of Fig. 1.

[0965] VGAM17 RNA, herein schematically represented by VGAM1 RNA through VGAM3 RNA, binds complementarily to a host target binding site located in an untranslated region of VGAM17 host target RNA, herein schematically represented by VGAM1 HOST TARGET RNA through VGAM3 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM17 host target RNA into VGAM17 host target protein, herein schematically represented by VGAM1 HOST TARGET PROTEIN through VGAM3 HOST TARGET PROTEIN, all of Fig. 1.

[0966] VGAM18 RNA, herein schematically represented by VGAM1 RNA through VGAM3 RNA, binds complementarily to a host target binding site located in an untranslated region of VGAM18 host target RNA, herein schematically represented by VGAM1 HOST TARGET RNA through VGAM3 HOST TARGET RNA, which host target binding site

corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM18 host target RNA into VGAM18 host target protein, herein schematically represented by VGAM1 HOST TARGET PROTEIN through VGAM3 HOST TARGET PROTEIN, all of Fig. 1.

[0967] VGAM19 RNA, herein schematically represented by VGAM1 RNA through VGAM3 RNA, binds complementarily to a host target binding site located in an untranslated region of VGAM19 host target RNA, herein schematically represented by VGAM1 HOST TARGET RNA through VGAM3 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM19 host target RNA into VGAM19 host target protein, herein schematically represented by VGAM1 HOST TARGET PROTEIN through VGAM3 HOST TARGET PROTEIN, all of Fig. 1.

[0968] VGAM20 RNA, herein schematically represented by VGAM1 RNA through VGAM3 RNA, binds complementarily to a host target binding site located in an untranslated region of VGAM20 host target RNA, herein schematically represented by VGAM1 HOST TARGET RNA through

VGAM3 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM20 host target RNA into VGAM20 host target protein, herein schematically represented by VGAM1 HOST TARGET PROTEIN through VGAM3 HOST TARGET PROTEIN, all of Fig. 1.

[0969] VGAM21 RNA, herein schematically represented by VGAM1 RNA through VGAM3 RNA, binds complementarily to a host target binding site located in an untranslated region of VGAM21 host target RNA, herein schematically represented by VGAM1 HOST TARGET RNA through VGAM3 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM21 host target RNA into VGAM21 host target protein, herein schematically represented by VGAM1 HOST TARGET PROTEIN through VGAM3 HOST TARGET PROTEIN, all of Fig. 1.

[0970] VGAM22 RNA, herein schematically represented by VGAM1 RNA through VGAM3 RNA, binds complementarily to a host target binding site located in an untranslated region of VGAM22 host target RNA, herein schematically

represented by VGAM1 HOST TARGET RNA through VGAM3 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM22 host target RNA into VGAM22 host target protein, herein schematically represented by VGAM1 HOST TARGET PROTEIN through VGAM3 HOST TARGET PROTEIN, all of Fig. 1.

[0971] It is appreciated that a function of VGR30 gene, herein designated VGR GENE, is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGR30 gene include diagnosis, prevention and treatment of viral infection by Human Immunodeficiency Virus 1. Specific functions, and accordingly utilities, of VGR30 gene correlate with, and may be deduced from, the identity of the host target genes, which are inhibited by VGAM RNAs comprised in the `operon-like` cluster of VGR30 gene: VGAM15 host target protein, VGAM16 host target protein, VGAM17 host target protein, VGAM18 host target protein, VGAM19 host target protein, VGAM20 host target protein, VGAM21 host target protein and VGAM22 host target protein, herein schematically represented by VGAM1 HOST TARGET PRO-

TEIN through VGAM3 HOST TARGET PROTEIN. The function of these host target genes is elaborated hereinabove with reference to VGAM15, VGAM16, VGAM17, VGAM18, VGAM19, VGAM20, VGAM21 and VGAM22. Fig. 9 further provides a conceptual description of novel bioinformatically detected regulatory viral gene, referred to here as Viral Genomic Record 31(VGR31) viral gene, which encodes an `operon-like` cluster of novel viral micro RNA-like genes, each of which in turn modulates expression of at least one host target gene, the function and utility of which at least one host target gene is known in the art.

[0972] VGR31 gene, herein designated VGR GENE, is a novel bioinformatically detected regulatory, non protein coding, RNA viral gene. The method by which VGR31 gene was detected is described hereinabove with reference to Figs. 1-9.

[0973] VGR31 gene encodes VGR31 precursor RNA, herein designated VGR PRECURSOR RNA, an RNA molecule, typically several hundred nucleotides long.

[0974] VGR31 precursor RNA folds spatially, forming VGR31 folded precursor RNA, herein designated VGR FOLDED PRECURSOR RNA. It is appreciated that VGR31 folded precursor RNA comprises a plurality of what is known in the

art as `hairpin` structures. These `hairpin` structures are due to the fact that the nucleotide sequence of VGR31 precursor RNA comprises a plurality of segments, the first half of each such segment having a nucleotide sequence which is at least a partial inversed-reversed sequence of the second half thereof, as is well known in the art.

[0975] VGR31 folded precursor RNA is naturally processed by cellular enzymatic activity into at least 7 separate VGAM precursor RNAs, VGAM23 precursor RNA, VGAM24 precursor RNA, VGAM25 precursor RNA, VGAM26 precursor RNA, VGAM27 precursor RNA, VGAM28 precursor RNA and VGAM29 precursor RNA, herein schematically represented by VGAM1 FOLDED PRECURSOR through VGAM3 FOLDED PRECURSOR, each of which VGAM precursor RNAs being a hairpin shaped RNA segment, corresponding to VGAM FOLDED PRECURSOR RNA of Fig. 1.

[0976] The above mentioned VGAM precursor RNAs are `diced` by DICER COMPLEX of Fig. 1, yielding respective short RNA segments of about 22 nucleotides in length, VGAM23 RNA, VGAM24 RNA, VGAM25 RNA, VGAM26 RNA, VGAM27 RNA, VGAM28 RNA and VGAM29 RNA, herein schematically represented by VGAM1 RNA through VGAM3 RNA, each of which VGAM RNAs corresponding to VGAM RNA of

Fig. 1.

[0977] VGAM23 RNA, herein schematically represented by VGAM1 RNA through VGAM3 RNA, binds complementarily to a host target binding site located in an untranslated region of VGAM23 host target RNA, herein schematically represented by VGAM1 HOST TARGET RNA through VGAM3 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM23 host target RNA into VGAM23 host target protein, herein schematically represented by VGAM1 HOST TARGET PROTEIN through VGAM3 HOST TARGET PROTEIN, all of Fig. 1.

[0978] VGAM24 RNA, herein schematically represented by VGAM1 RNA through VGAM3 RNA, binds complementarily to a host target binding site located in an untranslated region of VGAM24 host target RNA, herein schematically represented by VGAM1 HOST TARGET RNA through VGAM3 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM24 host target RNA into VGAM24 host target protein, herein schematically repre-

sented by VGAM1 HOST TARGET PROTEIN through VGAM3 HOST TARGET PROTEIN, all of Fig. 1.

[0979] VGAM25 RNA, herein schematically represented by VGAM1 RNA through VGAM3 RNA, binds complementarily to a host target binding site located in an untranslated region of VGAM25 host target RNA, herein schematically represented by VGAM1 HOST TARGET RNA through VGAM3 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM25 host target RNA into VGAM25 host target protein, herein schematically represented by VGAM1 HOST TARGET PROTEIN through VGAM3 HOST TARGET PROTEIN, all of Fig. 1.

[0980] VGAM26 RNA, herein schematically represented by VGAM1 RNA through VGAM3 RNA, binds complementarily to a host target binding site located in an untranslated region of VGAM26 host target RNA, herein schematically represented by VGAM1 HOST TARGET RNA through VGAM3 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM26 host target RNA into

VGAM26 host target protein, herein schematically represented by VGAM1 HOST TARGET PROTEIN through VGAM3 HOST TARGET PROTEIN, all of Fig. 1.

[0981] VGAM27 RNA, herein schematically represented by VGAM1 RNA through VGAM3 RNA, binds complementarily to a host target binding site located in an untranslated region of VGAM27 host target RNA, herein schematically represented by VGAM1 HOST TARGET RNA through VGAM3 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM27 host target RNA into VGAM27 host target protein, herein schematically represented by VGAM1 HOST TARGET PROTEIN through VGAM3 HOST TARGET PROTEIN, all of Fig. 1.

[0982] VGAM28 RNA, herein schematically represented by VGAM1 RNA through VGAM3 RNA, binds complementarily to a host target binding site located in an untranslated region of VGAM28 host target RNA, herein schematically represented by VGAM1 HOST TARGET RNA through VGAM3 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby

inhibiting translation of VGAM28 host target RNA into VGAM28 host target protein, herein schematically represented by VGAM1 HOST TARGET PROTEIN through VGAM3 HOST TARGET PROTEIN, all of Fig. 1.

[0983] VGAM29 RNA, herein schematically represented by VGAM1 RNA through VGAM3 RNA, binds complementarily to a host target binding site located in an untranslated region of VGAM29 host target RNA, herein schematically represented by VGAM1 HOST TARGET RNA through VGAM3 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM29 host target RNA into VGAM29 host target protein, herein schematically represented by VGAM1 HOST TARGET PROTEIN through VGAM3 HOST TARGET PROTEIN, all of Fig. 1.

[0984] It is appreciated that a function of VGR31 gene, herein designated VGR GENE, is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGR31 gene include diagnosis, prevention and treatment of viral infection by Human Immunodeficiency Virus 1. Specific functions, and accordingly utilities, of VGR31 gene correlate with, and

may be deduced from, the identity of the host target genes, which are inhibited by VGAM RNAs comprised in the `operon-like` cluster of VGR31 gene: VGAM23 host target protein, VGAM24 host target protein, VGAM25 host target protein, VGAM26 host target protein, VGAM27 host target protein, VGAM28 host target protein and VGAM29 host target protein, herein schematically represented by VGAM1 HOST TARGET PROTEIN through VGAM3 HOST TARGET PROTEIN. The function of these host target genes is elaborated hereinabove with reference to VGAM23, VGAM24, VGAM25, VGAM26, VGAM27, VGAM28 and VGAM29.

[0985] It is appreciated by persons skilled in the art that the present invention is not limited by what has been particularly shown and described hereinabove. Rather the scope of the present invention includes both combinations and subcombinations of the various features described hereinabove as well as variations and modifications which would occur to persons skilled in the art upon reading the specifications and which are not in the prior art.

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